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(54) Title: RIFAMYCIN BIOSYNTHESIS GENE CLUSTER

(57) Abstract

The present invention primarily relates to a DNA fragment which is obtainable from the gene cluster responsible for rifamycin biosynthesis within the genome of *Amycolatopsis mediterranei*, and comprises at least one gene or a part of a gene which codes for a polypeptide which is directly or indirectly involved in the biosynthesis of rifamycin, and to a method for preparing said DNA fragment. The present invention furthermore relates to recombinant DNA molecules which comprise one of the DNA fragments according to the invention, and to the plasmids and vectors derived therefrom. Host organisms transformed with said plasmid or vector DNA are likewise embraced.

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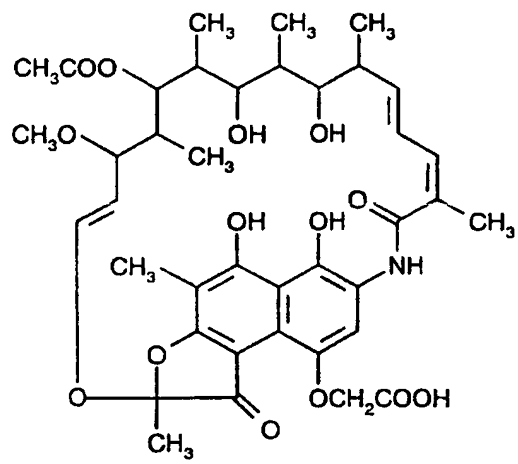
Rifamycin biosynthesis gene cluster

Rifamycins form an important group of macrocyclic antibiotics (Wehrli, Topics in Current Chemistry (1971), **72**, 21-49). They consist of a naphthoquinone chromophore which is spanned by a long aliphatic bridge. Rifamycins belong to the class of ansamycin antibiotics which are produced by several Gram-positive soil bacteria of the actinomycetes group and a few plants.

Ansamycins are characterized by a flat aromatic nucleus spanned by a long aliphatic bridge joining opposite positions of the nucleus. Two different groups of ansamycins can be distinguished by the structure of the aromatic nucleus. One group has a naphthoquinoid chromophore, with the typical representatives being rifamycin, streptovaricin, tolypomycin and naphthomycin. The second group, which has a benzoquinoid chromophore, is characterized by geldanamycin, maytansines and ansamitocines (Ghisalba et al., Biotechnology of Industrial Antibiotics Vandamme E. J. Ed., Decker Inc. New York, (1984) 281-327). In contrast to antibiotics of the macrolide type, the ansamycins contain in the aliphatic ring system not a lactone linkage but an amide linkage which forms the connection to the chromophore.

The discovery of the rifamycins produced by the microorganism *Streptomyces mediterranei* (as the organism was called at that time, see below) was described for the first time in 1959 (Sensi et al., Farmaco Ed. Sci. (1959) 14, 146-147). Extraction with ethyl acetate of the acidified cultures of *Streptomyces mediterranei* resulted in isolation of a mixture of antibiotically active components, the rifamycins A, B, C, D and E. Rifamycin B, the most stable component, was separated from the other components and isolated on the basis of its strongly acidic properties and ease of salt formation.

Rifamycin B has the structure of the formula (1)



(1)

Rifamycin B is the main component of the fermentation when barbiturate is added to the fermentation medium and/or improved producer mutants of *Streptomyces mediterranei* are used.

The rifamycin producer strain was originally classified as *Streptomyces mediterranei* (Sensi et al., Farmaco Ed. Sci. (1959) **14**, 146-147). Analysis of the cell wall of *Streptomyces mediterranei* by Thiemann et al. later revealed that this strain has a cell wall typical of *Nocardia*, and the strain was reclassified as *Nocardia mediterranei* (Thieman et al. Arch. Microbiol. (1969), **67** 147-151). *Nocardia mediterranei* has been reclassified again on the basis of more recent accurate morphological and biochemical criteria. Based on the exact composition of the cell wall, the absence of mycolic acid and the insensitivity to *Nocardia* and *Rhodococcus* phages, the strain has been assigned to the new genus *Amycolatopsis* as *Amycolatopsis mediterranei* (Lechevalier et al., Int. J. Syst. Bacteriol. (1986), 36, 29).

Rifamycins have a strong antibiotic activity mainly against Gram-positive bacteria such as mycobacteria, neisserias and staphylococci. The bactericidal effect of rifamycins derives from specific inhibition of the bacterial DNA-dependent RNA polymerase, which interrupts RNA biosynthesis (Wehrli and Staehelin, Bacteriol. Rev. (1971), **35**, 290-309). The semisynthetic rifamycin B derivative rifampin (rifampicin) is widely used clinically as antibiotic against the agent causing tuberculosis, *Mycobacterium tuberculosis*.

The naphthoquinoid ansamycins of the streptovaricin and tolypomycin group show, like rifamycin, an antibacterial effect by inhibiting bacterial RNA polymerase. By contrast, naphthomycin has an antibacterial effect without inhibiting bacterial RNA polymerase. The

benzoquinoid ansamycins show no inhibition of bacterial RNA polymerase, and they therefore have only relatively weak antibacterial activity, if any. On the other hand, some representatives of this class of substances have an effect on eukaryotic cells. Thus, antifungal, antiprotozoal and antitumour properties have been described for geldanamycin. On the other hand, antimitotic (antitubilin), antileukaemic and antitumour properties are ascribed to the maytansines. Some rifamycins also show antitumour and antiviral activity, but only at high concentrations. This biological effect thus appears to be nonspecific.

Despite the great structural variety of the ansamycins, their biosynthesis appears to take place by a metabolic pathway which contains many common elements (Ghisalba et al. Biotechnology of Industrial Antibiotics Vandamme E. J. Ed., Decker Inc. New York, (1984) 281-327). The aromatic nucleus for all ansamycins is probably built up starting from 3-amino-5-hydroxybenzoic acid. Starting from this molecule, which is presumably activated as coenzyme A, the entire aliphatic bridge is synthesized by a multifunctional polyketide synthase. The length of the bridge and the processing of the keto groups, which are initially formed by the condensation steps, are controlled by the polyketide synthase. To build up the complete aliphatic bridge for rifamycins, 10 condensation steps, 2 with acetate and 8 with propionate as building blocks, are necessary. The sequence of these individual condensation steps is likewise determined by the polyketide synthase. Structural comparisons and studies with incorporation of radioactive acetate and propionate have shown that the sequence of acetate and propionate incorporation for the various ansamycins takes place in accordance with a scheme which appears to be identical or very similar in the first condensation steps. Thus, from a common synthesis scheme of the ansamycin polyketide synthases (the rifamycin synthesis scheme), the syntheses of the various ansamycins sooner or later branch off, in accordance with their structural difference from the rifamycin structure, into side branches of the synthesis (Ghisalba et al., Biotechnology of Industrial Antibiotics Vandamme E. J. Ed., Decker Inc. New York, (1984) 281-327).

Because of the great structural variety of the rifamycins and their specific and interesting biological effect, there is great interest in understanding the genetic basis of their synthesis in order to create the possibility of specifically influencing it. This is particularly desirable because, as explained above, there is much in common between the synthesis of rifamycins and that of other ansamycins. This similarity in the biosynthesis, which probably derives from a common evolutionary origin of this metabolic pathway, naturally has a genetic basis.

The genetic basis of secondary metabolite biosynthesis essentially exists in the genes which code for the individual biosynthetic enzymes, and in the regulatory elements which control the expression of the biosynthesis genes. The secondary metabolite synthesis genes of actinomycetes have hitherto been found as clusters of adjacent genes in all the systems investigated. The size of such antibiotic gene clusters extends from about 10 kilobases (kb) up to more than 100 kb. The clusters often contain specific regulator genes and genes for resistance of the producer organism to its own antibiotic (Chater, Ciba Found. Symp. (1992), 171, 144-162).

The invention described herein has now succeeded, by identifying and cloning genes of rifamycin biosynthesis, in creating the genetic basis for synthesizing by genetic methods rifamycin analogues or novel ansamycins which combine structural elements from rifamycin with other ansamycins. This also creates the basis for preparing novel collections of substances based on the rifamycin biosynthesis gene cluster by combinatorial biosynthesis.

It was possible in a first step to identify and clone a DNA fragment from the genome of *A. mediterranei*, which shows homology with known polyketides synthase genes. After obtaining the sequence information from this DNA fragment which confirmed a typical sequence for polyketide synthases it was possible to screen a cosmid library of *A. mediterranei* with specific DNA probes derived from this fragment in a screening program for further DNA fragments which are involved in the rifamycin gene cluster. As a result, the complete rifamycin polyketide synthase gene cluster was identified and subjected to sequence determination (see SEQ ID NO 3). The gene cluster comprises six open reading frames, which are referred to hereinafter as ORF A, B, C, D, E and F and which code for the proteins and polypeptides depicted in SEQ ID NOS 4 to 9.

The gene cluster isolated and characterized in this way represents the basis, for example, for targeted optimization of the production of rifamycin, ansamycins or analogues thereof. Examples of techniques and possible areas of application available in this connection are as follows:

- Overexpression of individual genes in producer strains with plasmid vectors or by incorporation into the chromosome.
- Study of the expression and transcriptional regulation of the gene cluster during fermentation with various producer strains and optimization thereof through physiological parameters and appropriate fermentation conditions.

- Identification of regulatory genes and of the DNA binding sites of the corresponding regulatory proteins in the gene cluster. Characterization of the effect of these regulatory elements on the production of rifamycins or ansamycins; and influencing them by specific mutation in these genes or the DNA binding sites.
- Duplication of the complete gene cluster or parts thereof in producer strains.

Besides these applications of the gene cluster to improve production by fermentation as described above, it can likewise be employed for the biosynthetic preparation of novel rifamycin analogues or novel ansamycins or ansamycin-like compounds in which the aliphatic bridge is connected at only one end to the aromatic nucleus. The following possibilities come into consideration here, for example:

- Inactivation of individual steps in the biosynthesis, for example by gene disruption.
- Mutation of individual steps in the biosynthesis, for example by gene replacement.
- Use of the cluster or fragments thereof as DNA probe in order to isolate other natural microorganisms which produce metabolites similar to rifamycin or ansamycins.
- Exchange of individual elements in this gene cluster by those from other gene clusters.
- Use of modified polyketide synthases for setting up libraries of various rifamycin analogues or ansamycins, which are then tested for their activity (Jackie & Khosla, Chemistry & Biology, (1995), **2**, 355-362).
- Construction of mutated actinomycetes strains from which the natural rifamycin or ansamycin biosynthesis gene cluster in the chromosome has been partly or completely deleted, and can thus be used for expressing genetically modified gene clusters.
- Exchange of individual elements within the gene cluster.

Detailed description of the invention

The invention relates to a DNA fragment from the genome of *Amycolatopsis mediterranei*, which comprises a DNA region which is involved directly or indirectly in the gene cluster responsible for rifamycin synthesis; and the adjacent DNA regions; and functional constituents or domains thereof.

The DNA fragments according to the invention may moreover comprise regulatory sequences such as promoters, repressor or activator binding sites, repressor or activator genes, terminators; or structural genes. Likewise part of the invention are any combinations of these DNA fragments with one another or with other DNA fragments, for example combinations of promoters, repressor or activator binding sites and/or repressor or activator genes from an ansamycin gene cluster, in particular from the rifamycin gene cluster, with

foreign structural genes or combinations of structural genes from the ansamycin gene cluster, especially the rifamycin gene cluster, with foreign promoters; and combinations of structural genes with one another or with gene fragments which code for enzymatically active domains and are from various ansamycin biosynthesis systems. Foreign structural genes, and foreign gene fragments coding for enzymatically active domains, code, for example, for proteins involved in the biosynthesis of other ansamycins.

A preferred DNA fragment is one directly or indirectly involved in the gene cluster responsible for rifamycin synthesis.

The gene cluster or DNA region described above contains, for example, the genes which code for the individual enzymes involved in the biosynthesis of ansamycins and, in particular, of rifamycin, and the regulatory elements which control the expression of the biosynthesis genes. The size of such antibiotic gene clusters extends from about 10 kilobases (kb) up to over 100 kb. The gene clusters normally comprise specific regulatory genes and genes for resistance of the producer organism to its own antibiotic. Examples of what is meant by enzymes or enzymatically active domains involved in this biosynthesis are those necessary for synthesizing, starting from 3-amino-5-hydroxybenzoic acid, the ansamycins such as rifamycin, for example polyketide synthases, acyltransferases, dehydratases, ketoreductases, acyl carrier proteins or ketoacyl synthases.

Thus, the complete sequence of the gene cluster shown in SEQ ID NO 3, as well as DNA fragments which comprise sequence portions which code for a polyketide synthase or an enzymatically active domain thereof, are particularly preferred. Examples of such preferred DNA fragments are, for example, those which code for one or more of the proteins and polypeptides depicted in SEQ ID ID NOS 4, 5, 6, 7, 8 and 9, or functional derivatives thereof, also including partial sequences thereof which comprise, for example, 15 or more consecutive nucleotides. Other preferred embodiments relate to DNA regions of the gene cluster according to the invention or fragments thereof, like those present in the deposited clones pNE95, pRi44-2 and pNE112, or derived therefrom. Further preferred DNA fragments are those comprising sequence portions which display homologies with the sequences comprised by the clones pNE95, pRi44-2 and/or pNE112 or with SEQ ID ID NOS 1 and/or 3, and therefore can be used as hybridization probe within a genomic gene bank of an ansamycin-, in particular, rifamycin-producing organism for finding constituents

of the corresponding gene cluster. The DNA fragment may moreover, for example, comprise exclusively genomic DNA. A particularly preferred DNA fragment is one which comprises the nucleotide sequence depicted in SEQ ID NO 1 or 3, or partial sequences thereof, which, by reason of homologies, can be regarded as structural or functional equivalent to said sequence or partial sequence therefrom, and which therefore are able to hybridize with this sequence.

The DNA fragments according to the invention comprise, for example, sequence portions which comprise homologies with the above-described enzymes, enzyme domains or fragments thereof.

The term homologies and structural and/or functional equivalents refers primarily to DNA and amino acid sequences with few or minimal differences between the relevant sequences. These differences may have very diverse causes. Thus, for example, this may entail mutations or strain-specific differences which occur naturally or are artificially induced. Or the differences observed from the initial sequence are derived from a targeted modification, which can be introduced, for example, during a chemical synthesis.

Functional differences can be regarded as minimal if, for example, the nucleotide sequence coding for a polypeptide, or a protein sequence has essentially the same characteristic properties as the initial sequence, whether in respect of enzymatic activity, immunological reactivity or, in the case of a nucleotide sequence, gene regulation.

Structural differences can be regarded as minimal as long as there is a significant overlap or similarity between the various sequences, or they have at least similar physical properties. The latter include, for example, the electrophoretic mobility, chromatographic similarities, sedimentation coefficients, spectrophotometric properties etc.

In the case of nucleotide sequences, the agreement should be at least 70%, but preferably 80% and very particularly preferably 90% or more. In the case of the amino acid sequence, the corresponding figures are at least 50%, but preferably 60% and particularly preferably 70%. 90% agreement is very particularly preferred.

The invention furthermore relates to a method for identifying, isolating and cloning one of the DNA fragments described above. A preferred method comprises, for example, the following steps:

a) setting up of a genomic gene bank,

b) screening of this gene bank with the assistance of the DNA sequences according to the invention, and

c) isolation of the clones identified as positive.

A general method for identifying DNA fragments involved in the biosynthesis of ansamycins comprises, for example, the following steps

1) Cloning of a DNA fragment which shows homology with known polyketide synthase genes.

   a) The presence of DNA fragments having homology with the polyketide synthase genes according to the invention is detected in the strains of the microorganism to be investigated by a Southern experiment with chromosomal DNA of this strain. The size of such homologous DNA fragments can be determined by digesting the DNA with a suitable restriction enzyme.

   b) Production of a plasmid gene bank comprising the above digested chromosomal fragments. Normally, individual clones of this gene bank are tested once again for homology with the polyketide synthase genes according to the invention. Clones with recombinant plasmids comprising fragments having homology with the polyketide probe are then normally isolated on the basis of this homology.

2) Analysis of the cloned region

   a) Restriction analysis of the isolated recombinant plasmids and checking of the identity of these cloned fragments with one another.

   b) By a chromosomal Southern with DNA of the original microorganism and the isolated DNA fragment as probe it can be demonstrated that the cloned fragment is an original chromosomal DNA fragment from the original microorganism.

   c) It is possible as an option to demonstrate a significant homology of the cloned DNA fragment with chromosomal DNA from other ansamycin producers (streptovaricin, tolypomycin, geldanamycin, ansamitocin). This would confirm that the cloned DNA is typical of gene clusters of ansamycin biosynthesis and thus also of rifamycin biosynthesis.

d) DNA sequencing of an internal restriction fragment and demonstration by comparative sequence analysis that the cloned region is a typical DNA sequence of polyketide synthases, coding for the biosynthesis of polyketide antibiotics from actinomycetes.

3) Isolation and characterization of adjacent DNA regions

a) Construction of a cosmid gene bank from the original microorganism and analysis thereof for homology with the isolated fragments. Isolation of cosmids having homology with this fragment.

b) Demonstration by restriction analysis that the isolated cosmid clones comprise a DNA region of the original microorganism which overlaps with the original fragment.

As described above, the first step in the isolation of the DNA fragments according to the invention is normally the setting up of genomic gene banks from the organism of interest, which synthesize the required ansamycin, especially rifamycin.

Genomic DNA can be obtained from a host organism in various ways, for example by extraction from the nuclear fraction and purification of the extracted DNA by known methods.

The fragmentation, which is necessary for setting up a representative gene bank, of the genomic DNA to be cloned to a size which is suitable for insertion into a cloning vector can take place either by mechanical shearing or else, preferably, by cutting with suitable restriction enzymes.

Suitable cloning vectors, which are already in routine use for producing genomic gene libraries, comprise, for example, cosmid vectors, plasmid vectors or phage vectors.

It is then possible in a screening program to obtain suitable clones which comprise the required gene(s) or gene fragment(s) from the gene libraries produced in this way.

One possibility for identifying the required DNA region consists in, for example, using the gene bank described above to transform strains which, because of a blocked synthetic pathway, are unable to produce ansamycins, and identifying those clones which are again able after the transformation to produce ansamycin (revertants). The vectors which lead to revertants comprise a DNA fragment which is required in ansamycin synthesis.

Another possibility for identifying the required DNA region is based, for example, on using suitable probe molecules (DNA probe) which are obtained for example as described above. Various standard methods are available for identifying suitable clones, such as differential colony hybridization or plaque hybridization.

It is possible to use as probe molecule a previously isolated DNA fragment from the same or a structurally related gene or gene cluster which, because of the homologies present, is able to hybridize with the corresponding sequence section within the required gene or gene cluster to be identified. Preferably used as probe molecule for the purpose of the present invention is a DNA fragment obtainable from a gene or a DNA sequence involved in the synthesis of polyketides such as ansamycins or soraphens.

If the nucleotide sequence of the gene to be isolated, or at least parts of this sequence, are known, it is possible in an alternative embodiment to use, based on this sequence information, a corresponding synthesized DNA sequence for the hybridizations or PCR amplifications.

In order to facilitate detectability of the required gene or else parts of a required gene, one of the DNA probe molecules described above can be labelled with a suitable, easily detectable group. A detectable group for the purpose of this invention means any material which has a particular, easily identifiable, physical or chemical property.

Particular mention may be made at this point of enzymatically active groups such as enzymes, enzyme substrates, coenzymes and enzyme inhibitors, furthermore fluorescent and luminescent agents, chromophores and radioisotopes such as ^{3}H, ^{35}S, ^{32}P, ^{125}I and ^{14}C. Easy detectability of these markers is based, on the one hand, on their intrinsic physical properties (for example fluorescent markers, chromophores, radioisotopes) or, on the other hand, on their reaction and binding properties (for example enzymes, substrates, coenzymes, inhibitors). Materials of these types are already widely used in particular in immunoassays and, in most cases, can also be used in the present application.

General methods relating to DNA hybridization are described, for example, by Maniatis T. *et al.*, Molecular Cloning, Cold Spring Harbor Laboratory Press (1982).

Those clones within the previously described gene libraries which are able to hybridize with a probe molecule and which can be identified by one of the abovementioned detection methods can then be further analysed in order to determine the extent and nature of the coding sequence in detail.

An alternative method for identifying cloned genes is based on constructing a gene library consisting of plasmid or expression vectors. This entails, in analogy to the methods described previously, the genomic DNA comprising the required gene being initially isolated and then cloned into a suitable plasmid or expression vector. The gene libraries produced in this way can then be screened by suitable procedures, for example by use of complementation studies, and those clones which comprise the required gene or else at least a part of this gene as insert can be selected.

It is thus possible with the aid of the methods described above to isolate a gene, several genes or a gene cluster which code for one or more particular gene products.

For further characterization, the DNA sequences purified and isolated in the manner described above are subjected to restriction analysis and sequence analysis.

For sequence analysis, the previously isolated DNA fragments are first fragmented using suitable restriction enzymes, and then cloned into suitable cloning vectors. In order to avoid mistakes in the sequencing, it is advantageous to sequence both DNA strands completely.

Various alternatives are available for analysing the cloned DNA fragment in respect of its function within ansamycin biosynthesis.

Thus, for example, it is possible in complementation experiments with defective mutants not only to establish involvement in principle of a gene or gene fragment in secondary metabolite biosynthesis, but also to verify specifically the synthetic step in which said DNA fragment is involved.

In an alternative type of analysis, evidence is obtained in exactly the opposite way. Transfer of plasmids which comprise DNA sections which have homologies with appropriate sections

on the genome results in integration of said homologous DNA sections via homologous recombination. If, as in the present case, the homologous DNA section is a region within an open reading frame of the gene cluster, plasmid integration results in inactivation of this gene by so-called gene disruption and, consequently, in an interruption in secondary metabolite production. It is assumed according to current knowledge that a homologous region which comprises at least 100 bp, but preferably more than 1000 bp, is sufficient to bring about the required recombination event.

However, a homologous region which extends over a range of from 0.3 to 4 kb, but in particular over a range of from 1 to 3 kb, is preferred.

To prepare suitable plasmids which have sufficient homology for integration via homologous recombination there is preferably provision of a subcloning step in which the previously isolated DNA is digested, and fragments of suitable size are isolated and subsequently cloned into a suitable plasmid. Examples of suitable plasmids are the plasmids generally used for genetic manipulations in streptomycetes or *E. coli*.

It is possible in principle to use for the preparation and multiplication of the previously described constructs all conventional cloning vectors such as plasmid or bacteriophage vectors as long as they have replication and control sequences derived from species compatible with the host cell.

The cloning vector usually has an origin of replication plus specific genes which result in phenotypical selection features in the transformed host cell, in particular resistances to antibiotics. The transformed vectors can be selected on the basis of these phenotypical markers after transformation in a host cell.

Selectable phenotypical markers which can be used for the purpose of this invention comprise, for example, without this representing a limitation of the subject-matter of the invention, resistances to thiostrepton, ampicillin, tetracycline, chloramphenicol, hygromycin, G418, kanamycin, neomycin and bleomycin. Another selectable marker can be, for example, prototrophy for particular amino acids.

Mainly preferred for the purpose of the present invention are streptomycetes and *E. coli* plasmids, for example the plasmids used for the purpose of the present invention.

Host cells primarily suitable for the previously described cloning for the purpose of this invention are prokaryotes, including bacterial hosts such as streptomycetes, actinomycetes, *E. coli* or pseudomonads.

E. coli hosts are particularly preferred, for example the *E. coli* strain HB101 or X-1 blue MR®(Stratagene) or streptomyces such as the plasmid-free strains of *Streptomyces lividans* TK23 and TK24.

Competent cells of the *E. coli* strain HB101 are produced by the methods normally used for transforming *E. coli*. The transformation method of Hopwood *et al.* (Genetic manipulation of streptomyces a laboratory manual. The John Innes Foundation, Norwich (1985)) is normally used for streptomyces.

After transformation and subsequent incubation on a suitable medium, the resulting colonies are subjected to a differential screening by plating out on selective media. It is then possible to isolate the appropriate plasmid DNA from those colonies which comprise plasmids with DNA fragments cloned in.

The DNA fragment according to the invention, which comprises a DNA region which is involved directly or indirectly in the biosynthesis of ansamycin and can be obtained in the previously described manner from the ansamycin biosynthesis gene cluster, can also be used as starter clone for identifying and isolating other adjacent DNA regions overlapping therewith from said gene cluster.

This can be achieved, for example, by carrying out a so-called chromosome walking within a gene library consisting of DNA fragments with mutually overlapping DNA regions, using the previously isolated DNA fragment or else, in particular, the sequences located at its 5' and 3' margins. The procedures for chromosome walking are known to the person skilled in this art. Details can be found, for example, in the publications by Smith *et al.* (Methods

Enzymol (1987), **151**, 461-489) and Wahl *et al.* (Proc Natl. Acad. Sci, USA (1987), **84**, 2160-2164).

The prerequisite for chromosome walking is the presence of clones having coherent DNA fragments which are as long as possible and mutually overlap within a gene library, and a suitable starter clone which comprises a fragment which is located in the vicinity or else, preferably, within the region to be analysed. If the exact location of the starter clone is unknown, the walking is preferably carried out in both directions.

The actual walking step starts by using the identified and isolated starter clone as probe in one of the previously described hybridization reactions in order to detect adjacent clones which have regions overlapping with the starter clone. It is possible by hybridization analysis to establish which fragment projects furthest over the overlapping region. This is then used as starting clone for the 2nd walking step, in which case there is establishment of the fragment which overlaps with said 2nd clone in the same direction. Continuous progression in this manner on the chromosome results in a collection of overlapping DNA clones which cover a large DNA region. These can then, where appropriate after one or more subcloning steps, be ligated together by known methods to give a fragment which comprises parts or else, preferably all of the constituents essential for ansamycin biosynthesis.

The hybridization reaction to establish clones with overlapping marginal regions preferably makes use not of the very large and unwieldy complete fragment but, in its place, a partial fragment from the left or right marginal region, which can be obtained by a subcloning step. Because of the smaller size of said partial fragment, the hybridization reaction results in fewer positive hybridization signals, so that the analytical effort is distinctly less than on use of the complete fragment. It is furthermore advisable to characterize the partial fragment in detail in order to preclude its comprising larger amounts of repetitive sequences, which may be distributed over the entire genome and thus would greatly impede a targeted sequence of walking steps.

Since the gene cluster responsible for ansamycin biosynthesis covers a relatively large region of the genome, it may also be advantageous to carry out a so-called large-step walking or cosmid walking. It is possible in these cases, by using cosmid vectors which

permit the cloning of very large DNA fragments, to cover a very large DNA region, which may comprise up to 42 kb, in a single walking step.

In one possible embodiment of the present invention, for example, to construct a cosmid gene bank from streptomycetes or actinomycetes, complete DNA is isolated with the size of the DNA fragments being of the order of about 100 kb, and is subsequently partially digested with suitable restriction endonucleases.

The digested DNA is then extracted in a conventional way in order to remove endonuclease which is still present, and is precipitated and finally concentrated. The resulting fragment concentrate is then fractionated, for example by density gradient centrifugation, in accordance with the size of the individual fragments. After the fractions obtainable in this way have been dialysed they can be analysed on an agarose gel. The fractions which contain fragments of suitable size are pooled and concentrated for further processing. Fragments to be regarded as particularly suitable for the purpose of this invention have a size of the order of 30 kb to 42 kb, but preferably of 35 kb to 40 kb.

In parallel with the fragmentation described above, or later, for example a suitable cosmid vector pWE15® (Stratagene) is completely digested with a suitable restriction enzyme, for example BamHI, for the subsequent ligase reaction.

Ligation of the cosmid DNA to the streptomyces or actinomycetes fragments which have been fractionated according to their size can be carried out using a T4 DNA ligase. The ligation mixture obtainable in this way is, after a sufficient incubation time, packaged into λ phages by generally known methods.

The resulting phage particles are then used to infect a suitable host strain. A recA$^-$ *E. coli* strain is preferred, such as *E. coli* HB101 or X-1 Blue® (Stratagene). Selection of transfected clones and isolation of the plasmid DNA can be carried out by generally known methods.

The screening of the gene bank for DNA fragments which are involved in ansamycin biosynthesis is carried out, for example, using a specific hybridization probe which is assumed (for example on the basis of DNA sequence or DNA homology or

complementation tests or gene disruption or the function thereof in other organisms) to comprise DNA regions from the 'ansamycin gene cluster'.

A plasmid which comprises an additional fragment of the required size or has been identified on the basis of hybridizations can then be isolated from the gel in the previously described manner. The identity of this additional fragment with the required fragment of the previously selected cosmid can then be confirmed by Southern transfer and hybridization.

Function analysis of the DNA fragments isolated in this way can be carried out in a gene disruption experiment as described above.

Another possible use of the DNA fragments according to the invention is to modify or inactivate enzymes or domains involved in ansamycin and, in particular, rifamycin biosynthesis, or to synthesize oligonucleotides which are then in turn used for finding homologous sequences in PCR amplification.

Besides the DNA fragments according to the invention as such, also claimed are their use firstly for producing rifamycin, rifamycin analogues or precursors thereof, and for the biosynthetic production of novel ansamycins or of precursors thereof. Included in this connection are those molecules in which the aliphatic bridge is connected only at one end to the aromatic nucleus.

The DNA fragments according to the invention permit, for example, by combination with DNA fragments from other biosynthetic pathways or by inactivation or modification thereof, the biosynthesis of novel hybrid compounds, in particular of novel ansamycins or rifamycin analogues. The steps necessary for this are generally known and are described, for example, in Hopwood, Current Opinion in Biotechnol. (1993), **4**, 531-537.

The invention furthermore relates to the use of the DNA fragments according to the invention for carrying out the novel technology of combinatorial biosynthesis for the biosynthetic production of libraries of polyketide synthases based on the rifamycin and ansamycin biosynthesis genes. If, for example, several sets of modifications are produced, it is possible in this way to produce, by means of biosyntheses, a library of polyketides, for example ansamycins or rifamycin analogues, which then needs to be tested only for the

activity of the compounds produced in this way. The steps necessary for this are generally known and are described, for example, in Tsoi and Khosla, Chemistry & Biology (1995), **2**, 355-362 and WO-9508548.

Besides the DNA fragment as such, also claimed is its use for the genetic construction of mutated actinomycetes strains from which the natural rifamycin or ansamycin biosynthesis gene cluster in the chromosome has been partly or completely deleted, and which can thus be used for expressing genetically modified ansamycin or rifamycin biosynthesis gene clusters.

The invention furthermore relates to a hybrid vector which comprises at least one DNA fragment according to the invention, for example a promoter, a repressor or activator binding site, a repressor or activator gene, a structural gene, a terminator or a functional part thereof. The hybrid vector comprises, for example, an expression cassette which comprises a DNA fragment according to the invention which is able to express one or more proteins involved in ansamycin biosynthesis and, in particular in rifamycin biosynthesis, or a functional fragment thereof. The invention likewise relates to a host organism which comprises the hybrid vector described above.

Suitable vectors representing the starting point of the hybrid vectors according to the invention, and suitable host organisms such as bacteria or yeast cells are generally known.

The host organism can be transformed by generally customary methods such as by means of protoplasts, Ca^{2+}, Cs^{+}, polyethylene glycol, electroporation, viruses, lipid vesicles or a particle gun. The DNA fragments according to the invention may then be present both as extrachromosomal constituents in the host organism and integrated via suitable sequence sections into the chromosome of the host organism.

The invention likewise relates to polyketide synthases which comprise the DNA fragments according to the invention, in particular those from *Amycolatopsis mediterranei* which are involved directly or indirectly in rifamycin synthesis, and functional constituents thereof, for example enzymatically active domains.

The invention furthermore relates to a hybridization probe comprising a DNA fragment according to the invention, and to the use thereof, in particular for identifying DNA fragments involved in the biosynthesis of ansamycins.

In order to obtain unambiguous signals in the hybridization, DNA bound to the filter (for example made of nylon or nitrocellulose) is normally washed at 55-65°C in 0.2 × SSC (1 × SSC = 0.15 M sodium chloride, 15 mM sodium citrate).

Examples

General

General molecular genetic techniques such as DNA isolation and purification, restriction digestion of DNA, agarose gel electrophoresis of DNA, ligation of restriction fragments, cultivation and transformation of *E. coli*, plasmid isolation from *E. coli*, are carried out as described in Maniatis et al., Molecular Cloning: A laboratory manual, 1st Edit. Cold Spring Harbor Laboratory Press, Cold Spring Harbor NY (1982).

Culture conditions and molecular genetic techniques with *A. mediterranei* and other *actinomycetes* are as described by Hopwood *et al.* (Genetic manipulation of streptomyces a laboratory manual, The John Innes Foundation, Norwich, 1985). All liquid cultures of *A. mediterranei* and other *actinomycetes* are carried out in Erlenmeyer flasks at 28°C on a shaker at 250 rpm.

Nutrient media used:

LB Maniatis et al., Molecular Cloning: A laboratory manual, 1st Edit. Cold Spring Harbor Laboratory Press, Cold Spring Harbor NY (1982)

NL148 Schupp + Divers FEMS Microbiology Lett. **36**, 159-162 (1986) (NL148 = NL148G without glycine)

R2YE Hopwood *et al.* (Genetic manipulation of streptomyces a laboratory manual. The John Innes Foundation, Norwich, 1985)

TB :	12 g/l	Bacto tryptone
	24 g/l	Bacto yeast extract
	4 ml/l	glycerol

Example 1: Detection of chromosomal DNA fragments from *A. mediterranei* having homology with polyketide synthase genes of other bacteria

To obtain genomic DNA from *A. mediterranei*, cells of the strain *A. mediterranei* wt3136 (= LBGA 3136, ETH collection of strains) are cultivated in NL148 medium for 48 hours. 1 ml of this culture is then transferred into 50 ml of NL148 medium (+ 2.5 g/l glycine) in a 200 ml Erlenmeyer flask, and the culture is incubated for 48 h. The cells are removed from the medium by centrifugation at 3000 g for 10 min. and are resuspended in 5 ml of SET (75 mM NaCl, 25 mM EDTA, 20 mM Tris, pH 7.5). High molecular weight DNA is extracted by the method of Pospiech and Neumann (Trends in Genetics (1995), **11**, 217-218).

In order to detect, by a Southern blot, individual fragments from the isolated *A. mediterranei* DNA which have homology with polyketide synthase genes, a radioactive DNA probe is prepared from a known polyketide synthase gene cluster. To do this, the PvuI fragment 3.8 kb in size is isolated from the recombinant plasmid p98/1 (Schupp et al. J. of Bacteriol. (1995), **177**, 3673-3679), which comprises a DNA region, about 32 kb in size, from the polyketide synthase for the antibiotic soraphen A. About 0.5 μg of the isolated 3.8 kb PvuI DNA fragment is radiolabelled with ^{32}P-d-CTP by the nick translation system from Gibco/BRL (Basle) in accordance with the manufacturer's instructions.

For the Southern blot, about 2 μg of the genomic DNA isolated above from *A. mediterranei* are completely digested with the restriction enzyme BglII (Böhringer, Mannheim), and the resulting fragments are fractionated on a 0.8% agarose gel. A Southern blot with this agarose gel and the DNA probe isolated above (3.8 kb PvuI fragment) detects a DNA BglII-cut fragment which is about 13 kb in size from the genomic DNA of *A. mediterranei*, and which has homology with the DNA probe used. It can be concluded on the basis of this homology that the detected DNA fragment from *A. mediterranei* is a genetic region which codes for a polyketide synthase and thus is involved in the synthesis of a polyketide antibiotic.

Example 2: Production of a specific recombinant plasmid collection comprising BglII-digested chromosomal fragments from *A. mediterranei* 12-16 kb in size

The *E. coli* positive selection vector pIJ4642 (derivative of pIJ666, Kieser & Melton, Gene (1988), **65**, 83-91) developed at the John Innes Centre (Norwich, UK) is used to produce the plasmid gene bank. This plasmid is first cut with BamHI, and the two resulting fragments are fractionated on an agarose gel. The smaller of the two fragments is the filler fragment of the vector and the larger is the vector portion which, on self-ligation after deletion of the filler fragment, forms, owing to the flanking fd termination sequences, a perfect palindrome, which means that the plasmid cannot be obtained as such in *E. coli*. This vector portion 3.8 kb in size is isolated from the agarose gel by electroelution as described on page 164-165 of Maniatis et al., Molecular Cloning: A laboratory manual, 1st Edit. Cold Spring Harbor Laboratory Press, Cold Spring Harbor NY (1982).

To prepare the BglII-cut DNA fragments from *A. mediterranei*, the high molecular weight genomic DNA prepared in Example 1 is used. About 10 µg of this DNA are completely digested with the restriction enzyme BglII and subsequently fractionated on a 0.8% agarose gel. DNA fragments with a size of about 12 - 16 kb are cut out of the gel and detached from the gel block by electroelution (see above). About 1 µg of the BglII fragments isolated in this way is ligated to about 0.1 µg of the BamHI portion, isolated above, of the vector pIJ4642. The ligation mixture obtained in this way is then transformed into the *E. coli* strain HB101 (Stratagene). About 150 transformed colonies are selected from the transformation mixture on LB agar with 30 µg per ml chloramphenicol. These colonies contain recombinant plasmids with BglII-cut genomic DNA fragments from *A. mediterranei* in the size range 12 - 16 kb.

Example 3: Cloning and characterization of chromosomal *A. mediterranei* DNA fragments having homology with bacterial polyketide synthase genes

150 of the plasmid clones prepared in Example 2 are analysed by colony hybridization using a nitrocellulose filter (Schleicher & Schuell) as described on pages 318-319 of Maniatis et al., Molecular Cloning: A laboratory manual, 1st Edit. Cold Spring Harbor Laboratory Press, Cold Spring Harbor NY (1982). The DNA probe used is the 3.8 kb PvuI fragment, radiolabelled with ^{32}P-d-CTP and isolated in Example 1, of the plasmid p98/1. The plasmids are isolated from 5 plasmid clones which show a hybridization signal, and are characterized by two restriction digestions with the enzymes HindIII or KpnI. HindIII cuts

twice in the vector portion of the clones, 0.3 kb to the right and left of the BamHI cleavage site into which the *A. mediterranei* DNA has been integrated. KpnI does not cut in the pIJ 4642 vector portion. This restriction analysis shows that the investigated clones comprise both identical HindIII fragments of about 14 and 3.1 kb and identical KpnI fragments approximately 11.4 kb and 5.7 kb in size. This shows that these clones comprise the same genomic BglII fragment of *A. mediterranei*, and that the latter has a size of about 13 kb. It can additionally be concluded from this restriction analysis that this cloned BglII fragment has no internal HindIII cleavage site, but has 2 KpnI cleavage sites which afford an internal KpnI fragment 5.7 kb in size.

The plasmid DNA of the above 5 clones with identical restriction fragments is further characterized by a Southern blot. For this purpose, the plasmids are cut with HindIII and KpnI, and the DNA probe used is the ^{32}P-radiolabelled 3.8 kb PvuI fragment of the plasmid p98/1 used above. This experiment confirms that the 5 plasmids contain identical *A. mediterranei* DNA fragments and that these have significant homology with the DNA probe which is characteristic of bacterial polyketide synthase genes. In addition, the Southern blot shows that the internal KpnI fragment 5.7 kb in size likewise has significant homology with the DNA probe used. The plasmid called pRi7-3 is selected from the 5 plasmids for further processing.

To demonstrate that the cloned BglII fragment about 13 kb in size from *A. mediterranei* is an original chromosomal DNA fragment, another Southern blot is carried out. Chromosomal DNA from *A. mediterranei* which has been cut with BglII, KpnI or BamHI is employed in this blot. Two BamHI fragments which are about 1.8 and 1.9 kb in size and are present in the 5.7 kb KpnI fragment of pRi7-3 are used as radiolabelled DNA probe. This experiment confirms that the BglII DNA fragment about 13 kb in size cloned in the recombinant plasmid pRi7-3 is an authentic genomic DNA fragment from *A. mediterranei*. In addition, this experiment confirms that the cloned fragment comprises an internal KpnI fragment 5.7 kb in size and two BamHI fragments about 1.8 and 1.9 kb in size, and that these DNA fragments are likewise authentic genomic DNA fragments from *A. mediterranei*.

Example 4: Demonstration of a significant homology of the cloned genomic 13 kb BglII fragment from *A. mediterranei* with chromosomal DNA from other *actinomycetes* which produce ansamycins

Demonstration of a significant homology between the cloned chromosomal DNA region of *A. mediterranei* and chromosomal DNA from other ansamycin-producing actinomycetes takes place by a Southern blot experiment. The following ansamycin-producing strains are employed for this purpose (the ansamycins produced by the strains are in parentheses): *Streptomyces spectabilis* (streptovaricins), *Streptomyces tolypophorus* (tolypomycins), *Streptomyces hygroscopicus* (geldanamycins), *Nocardia species* ATCC31281 (ansamitocins). Genomic DNA from these strains is isolated as described for *A. mediterranei* in Example 1 and digested with the restriction enzyme KpnI, and the restriction fragments obtained in this way are fractionated on an agarose gel for the Southern blot. Two BamHI fragments about 1.8 and 1.9 kb in size from *A. mediterranei*, which are used in Example 3 and are isolated from the plasmid pRi7-3, are used as radioactive probe. This experiment shows that these ansamycin-producing strains have a significant DNA homology with the DNA probe used and thus with the cloned chromosomal region of *A. mediterranei*. It is to be observed in this connection that the homology in the case of producers of ansamycins with a naphthoquinoid ring system (streptovaricin, tolypomycin) is greater than in the case of those with a benzoquinoid ring system (geldanamycin, ansamitocin). This result suggests that the cloned chromosomal DNA region from *A. mediterranei* is typical of ansamycin biosynthesis gene clusters and, especially, of gene clusters for ansamycins with naphthoquinoid ring systems, corresponding to the ring system in rifamycins.

Example 5: DNA sequence determination of the KpnI fragment 5.7 kb in size located within the cloned 13 kb BglII fragment

For the sequencing, the 5.7 kb KpnI fragment is isolated from the plasmid pRi7-3 (DSM 11114) (Maniatis et. al. 1992) and subcloned into the KpnI cleavage site of the vector pBRKanf4, which is suitable for the DNA sequencing, affording the plasmids pTS004 and pTS005. The vector pBRKanf4 (derived from pBRKanf1; Bhat, Gene (1993) **134**, 83-87) is suitable for introducing sequential deletions of Sau3A fragments in the cloned insert fragment, because this vector does not itself have a GATC nucleotide sequence. In addition, the BamHI fragments 1.9 and 1.8 kb in size present in the 5.7 kb KpnI fragment are subcloned into the BamHI cleavage site of pBRKanf4, resulting the plasmids pTS006 and pTS007, and pTS008 and pTS009, respectively.

To prepare subclones sequentially truncated by Sau3A fragments for the DNA sequencing, the plasmids pTS004 to pTS009 are partially digested with Sau3A and completely digested with XbaI or HindIII (a cleavage site in the multiple cloning region of the vector). The DNA obtained in this way (consisting of the linearized vector with inserted DNA fragments truncated by Sau3A fragments) is filled in at the ends using Klenow polymerase (fragment of polymerase I, see Maniatis *et al.* pages 113-114), self-ligated with T4 DNA ligase and transformed into *E. coli* DH5α. The plasmid DNA which corresponds to the pTS004 to pTS009 plasmids, but has DNA regions, which are truncated from one side by Sau3A fragments, from the original integrated fragments of *A. mediterranei*, is isolated from individual transformed clones obtained in this way.

The DNA sequencing is carried out with the plasmids obtained in this way and with pTS004 to pTS009 using the reaction kit from Perkin-Elmer/Applied Biosystems with dye-labelled terminator reagents (Kit N° 402122) and a universal primer or a T7 primer. A standard cycle sequencing protocol with a thermocycler (MJ Research DNA Engine Thermocycler, Model 225) is used, and the sequencing reactions are analysed by the Applied Biosystems automatic DNA sequencer (Modell 373 or 377) in accordance with the manufacturer's instructions. To analyse the results, the following computer programs (software) are employed: Applied Biosystems DNA analysis software, Unix Solaris CDE software, DNA assembly and analysis package GAP licensed from R. Staden (Nucleic Acid Research (1995)23, 1406-1410) and Blast (NCBI).

The methods described above can be used to sequence completely both DNA strands of the 5.7 kb KpnI fragment from *A. mediterranei* strain wt3136. The DNA sequence of the 5.7 kb fragment with a length of 5676 base pairs is depicted in SEQ ID NO 1.

Example 6: Analysis of the protein-encoding region (genes) on the 5.7 kb KpnI fragment from *A. mediterranei*

The nucleotide sequence of the 5.7 kb KpnI fragment is analysed using the Codonpreference computer program (Genetics Computer Group, University of Wisconsin, 1994). This analysis shows that this fragment is over its whole length a protein-encoding region and thus forms part of a larger open reading frame (ORF). The codons used in this ORF are typical of

streptomycetes and actinomycetes genes. The amino acid sequence derived from the DNA sequence from this ORF is depicted in SEQ ID NO 2.

Polyketide synthases for macrolide antibiotics (such as erythromycin, rapamycin) are very large multifunctional proteins which comprise several enzymatically active domains which are now well characterized (Hopwood und Khosla, Ciba Foundation Symposium (1992), **171**, 88-112; Donadio and Katz, Gene (1992), **111**, 51-60; Schwecke et al., Proc. Natl. Acad. Sci. U.S.A. (1995) **92** (17), 7839-7843). Comparison of the amino acid sequence depicted in SEQ ID NO 2 with that of the very well-characterized erythromycin polyketide synthase, eryA ORF1 (Donadio, Science, (1991) 252, 675-679, DNA sequence gene/EMBL accession NO M63676) gives the following results:

Region from SEQ ID NO 2: amino acids 2 - 325: is 40% identical to the acyltransferase domain of module 2 of the *eryA* locus of *Saccharopolyspora erythraea*.

Region from SEQ ID NO 2: amino acids 325 - 470: is 43% identical to the dehydratase domain of module 4 of the *eryA* locus of *Saccharopolyspora erythraea*.

Region from SEQ ID NO 2: amino acids 762 - 940: is 48% identical to the ketoreductase domain of module 2 of the *eryA* locus of *Saccharopolyspora erythraea*.

Region from SEQ ID NO 2: amino acids 1024- 1109: is 57% identical to the acyl carrier protein domain of module 2 of the *eryA* locus of *Saccharopolyspora erythraea*.

Region from SEQ ID NO 2: amino acids 1126 - 1584: is 59% identical to the ketoacyl synthase domain of module 1 of the *eryA* locus of *Saccharopolyspora erythraea*.

The very large similarities found in the amino acid sequence and in the size and arrangement of the enzymatic domains suggest that the cloned KpnI region 5.7 kb in size from *A. mediterranei* codes for part of a polyketide synthase which is typical of polyketides of the macrolide type.

Example 7: Construction of a cosmid gene bank from *A. mediterranei*

The cosmid vector employed is the plasmid pWE15 which can be purchased (Stratagene, La Jolla, CA, USA). pWE15 is completely cut with the enzyme BamHI (Maniatis *et al.* 1989) and precipitated with ethanol. For ligation to the cosmid DNA, chromosomal DNA from *A. mediterranei* is isolated as described in Example 1 and partially digested with the restriction enzyme Sau3A (Böhringer, Mannheim) to form DNA fragments most of which have a size of 20 - 40 kb. The DNA pretreated in this way is fractionated by fragment size by centrifugation (83,000 g, 20°C) on a 10% to 40% sucrose density gradient for 18 h. The gradient is fractionated in 0.5 ml aliquots and dialysed, and samples of 10 µl are analysed on a 0.3% agarose gel with DNA size standard. Fractions with chromosomal DNA 25 - 40 kb in size are combined, precipitated with ethanol and resuspended in a small volume of water.

Ligation of the cosmid DNA to the *A. mediterranei* Sau3A fragments isolated according to their size (see above) takes place with the aid of a T4-DNA ligase. About 3 µg of each of the two DNA starting materials are employed in a reaction volume of 20 µl, and the ligation is carried out at 12°C for 15 h. 4 ml of this ligation mixture are packaged into lambda phages using the *in vitro* packaging kit which can be purchased from Stratagene (La Jolla, CA, USA) (in accordance with the manufacturer's instructions). The resulting phages are introduced by infection into the *E. coli* strain X-1BlueMR® (Stratagene). Titration of the phage material reveals about 20,000 phage particles per ml, analysis of 12 cosmid clones shows that all the clones contain plasmid DNA inserts 25 - 40 kb in size.

Example 8: Identification, cloning and characterization of the chromosomal *A. mediterranei* DNA region which is adjacent to the cloned 5.7 kb KpnI fragment

To identify and clone the chromosomal *A. mediterranei* DNA region which is adjacent to the 5.7 kb KpnI fragment described above in Examples 3 and 5, firstly a radioactive DNA probe is prepared from this 5.7 kb KpnI fragment. This is done by radiolabelling approximately 0.5 µg of the isolated DNA fragment with ^{32}P-d-CTP by the nick translation system of Gibco/BRL (Basle) in accordance with the manufacturer's instructions.

Infection of *E. coli* X-1 Blue MR (Stratagene) with an aliquot of the lambda phages packaged *in vitro* (see Example 7) results in more than 2000 clones on several LB + ampicillin (50 μg/ml) plates. These clones are tested by colony hybridization on nitrocellulose filters (see Example 3 for method). The DNA probe used is the 5.7 kb KpnI DNA fragment from *A. mediterranei* which is radiolabelled with ^{32}P-d-CTP and was prepared above.

5 cosmid clones showing a significant signal with the DNA probe are found. The plasmid DNA of these cosmids is isolated (Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989), digested with KpnI and analysed in an agarose gel. Analysis reveals that all 5 plasmids have integrated chromosomal *A. mediterranei* DNA with a size of the order of about 25-35 kb, and all contain the 5.7 kb KpnI fragment.

To characterize the chromosomal *A. mediterranei* DNA region which is adjacent to the cloned KpnI fragment, the plasmid DNA of one of the 5 cosmid clones is subjected to restriction analysis. The selected plasmid of the cosmid clone has the number pNE112 and likewise comprises the 13 kb BglII fragment described in Example 3.

Digestion of the plasmid pNE112 with the restriction enzymes BamHI, BglII, HindIII (singularly and in combination) allows a restriction map of the cloned region of *A. mediterranei* to be prepared, and this permits this region about 26 kb in size in the chromosome of *A. mediterranei* to be characterized. This region is characterized by the following restriction cleavage sites with the stated distance in kb from one end: BamHI in position 3.2 kb, HindIII in position 6.6 kb, BglII in position 11.5 kb, BamHI in position 16.6 kb, BamHI in position 17.3 kb, BamHI in position 21 kb and BglII in position 24 kb.

<u>Example 9:</u> <u>Determination of the sequence of the chromosomal *A. mediterranei* DNA region present in the plasmid pNE112 and overlapping with the cloned 5.7 kb KpnI fragment</u>

The plasmid pNE112 DNA is split up into fragments directly using an Aero-Mist nebulizer (CIS-US Inc., Bedford, MA, USA) under a nitrogen pressure of 8-12 pounds per square inch. These random DNA fragments are treated with T4 DNA polymerase, T4 DNA kinase and E. coli DNA polymerase in the presence of the 4 dNTPs in order to generate blunt ends

on the double-stranded DNA fragments (Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989). The fragments are then fractionated in 0.8% low melting agarose (FMC SeaPlaque Agarose, Catalogue N° 50113), and fragments 1.5-2 kb in size are extracted by hot phenol extraction (Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989). The DNA fragments obtained in this way are then ligated with the aid of T4 DNA ligase to the plasmid vector pBRKanf4 (see Example 5) or pBlueScript KS+ (Stratagene, La Jolla, CA, USA), each of which is cut once with square ends by appropriate restriction digestion (SmaI for pBRKanf4 and EcoRV for pBlueScript KS+), and is dephosphorylated on the ends by a treatment with alkaline phosphatase (Böhringer, Mannheim). The ligation mixture is then transformed into E. coli DH5α, and the cells are incubated overnight on LB agar with the appropriate antibiotic (kanamycin 40 μg/ml for pBRKanf4, ampicillin 100 μg/ml for pBlueScript KS+). Grown colonies are transferred singly into 1.25 ml of liquid TB medium with antibiotic in 96-well plates with wells of a volume of 2 ml, and incubated at 37°C overnight. Template DNA for the sequencing is prepared directly from these cultures by alkaline lysis (Birnboim, Methods in Enzymology (1983) 100, 243-255). The DNA sequencing takes place using the Perkin Elmer/Appied Biosystems reaction kit with dye-labelled terminator reagents (Kit N° 402122) and universal M13 mp18/19 primers or T3, T7 primers, or with primers prepared by us which bind to internal sequences. A standard cycle sequencing protocol with 20 cycles is used with a thermocycler (MJ Research DNA Engine Thermocycler, Model 225). The sequencing reactions are precipitated with ethanol, resuspended in formamide loading buffer and fractionated and analysed by electrophoresis using the Applied Biosystems automatic DNA sequencer (Model 377) in accordance with the manufacturer's instructions. Sequence files are produced with the aid of the Applied Biosystems DNA Analysis Software computer program and transferred to a SUN UltraSpark computer for further analysis. The following computer programs (software) are employed for analysing the results: DNA assembly and analysis package GAP (Genetics Computer Group, University of Wisconsin, R. Staden, Cambridge University UK) and the four programs: Phred, Cross-match, Phrad and Consed (P. Green, University of Washington, B. Ewing and D. Gordon, Washington University in Saint Louis). After the original sequences have been connected together to give longer coherent sequences (contigs), missing DNA sections are specifically sequenced with the aid of new primers (binding to sequenced sections), or by longer sequencing or sequencing the other strand.

It is possible with the method described above to sequence the entire chromosomal DNA region 26 kb in size from *A. mediterranei* which is cloned in pNE112. The DNA sequence is depicted in SEQ ID NO 3 in the base pair 27801 - 53789 section. The DNA sequence of the 5.7 kb KpnI fragment described in Example 5 is present in pNE112, and is depicted in SEQ ID NO 3 in the base pair 43093 - 48768 region.

Example 10: Identification and characterization of cosmid clones with chromosomal DNA fragments from *A. mediterranei* which overlap with one end of the 26 kb *A. mediterranei* region of pNE112

To identify cosmid clones which comprise chromosomal DNA fragments from *A. mediterranei* located directly in front of the 26 kb region of pNE112, the plasmid pNE112 is cut with the restriction enzyme BamHI, and the resulting BamHI fragment 3.2 kb in size is separated from the other BamHI fragments in an agarose gel and isolated from the gel. This BamHI fragment is located at one end of the incorporated *A. mediterranei* DNA in pNE112 (see Example 8) and can thus be used as DNA probe for finding the required cosmid clones. Approximately 0.5 μg of the isolated 3.2 kb BamHI DNA fragment is radiolabelled with ^{32}P-dCTP by the nick translation system from Gibco/BRL (Basel) in accordance with the manufacturer's instructions.

The cosmid gene bank from *A. mediterranei* described in Example 7 is then analysed by colony hybridization (Method of Example 3) using this 3.2 kb DNA probe for clones with overlaps. Two cosmid clones with a strong hybridization signal can be identified in this way and are given the numbers pNE95 and pRi44-2. It is possible by restriction analysis and Southern blot to confirm that the plasmids pNE95 and pRi44-2 comprise chromosomal DNA fragments from *A. mediterranei* which overlap with the 3.2 kb BamHI fragment from pNE112 and together cover a 35 kb chromosomal region of *A. mediterranei* which is directly adjacent to the 26 kb *A. mediterranei* fragment of pNE112 cloned in pNE112.

Example 11: Restriction analysis of the chromosomal *A. mediterranei* DNA region cloned with the cosmid clones pNE112, pNE95 and pRi44-2

The chromosomal *A. mediterranei* DNA region cloned with the cosmid clones pNE112, pNE95 and pRi44-2 is characterized by carrying out a restriction analysis. Digestion of the plasmid DNA of the three cosmids with the restriction enzymes EcoRI, BglII and HindIII (singly and in combination) produces a rough restriction map of the cloned region of *A. mediterranei*. Overlapping fragments of the three plasmids are in this case established and confirmed by Southern blot. This chromosomal region of *A. mediterranei* has a size of about 61 kb and is characterized by the following restriction cleavage sites with the stated distance in kb from one end: EcoRI in position 7.2 kb, HindIII in position 21 kb, BglII in position 31 kb, HindIII in position 42 kb, BglII in position 47 kb and BglII in position 59 kb. In this region in the *A. mediterranei* chromosome, the plasmid pRi 44-2 covers a region from position 1 to approximately 37 kb, plasmid pNE95 covers a region of approximate position 9 kb - 51 kb and plasmid pNE 112 covers a region of approximate position 35 kb - 61 kb.

Example 12: Determination of the sequence of the chromosomal *A. mediterranei* DNA region described in Example 11 from the EcoRI cleavage site in the 7.2 kb position up to the 61 kb end

Determination of the DNA sequence of the chromosomal region described in Example 11 from *A. mediterranei* (EcoRI cleavage site in the 7.2 kb position to 51 kb) is carried out with the plasmids pRi 44-2 and pNE95, using exactly the same method as described in Example 9. Analysis of the DNA sequence obtained in this way confirms the rough restriction map described in Example 11 and the overlaps of the cloned *A. mediterranei* fragments in the plasmids pNE112, pNE95 and pRi44-2.

The DNA sequence of the chromosomal *A. mediterranei* DNA region described in Example 11 from the EcoRI cleavage site in the 7.2 kb position up to the end at 61 kb is depicted in SEQ ID NO 3 (length 53789 base pairs).

Example 13: Analysis of a first protein-encoding region (ORF A) of the cloned *A. mediterranei* chromosomal region depicted in SEQ ID NO 3

The nucleotide sequence shown in SEQ ID NO 3 is analysed with the Codonpreference computer program (Genetics Computer Group, University of Wisconsin, 1994). This analysis shows that a very large open reading frame (ORF A) which codes for a protein is present in

the first third of the sequence (position 1825 - 15543 including stop codon in SEQ ID NO 3). The codons used in ORF A are typical of actinomycetes genes with a high G+C content.

Comparison of the amino acid sequence of ORF A (SEQ ID NO 4, size 4572 amino acids) with other polyketide synthases and specifically with the very well characterized polyketide synthase of *Saccharopolyspora erythraea* (Donadio, Science, (1991) 252, 675-679, DNA sequence gene/EMBL accession N° M63676) gives the following results:

Region from ORF A, SEQ ID NO 4: amino acids 370 - 451: is 50% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region from ORF A, SEQ ID NO 4: amino acids 469 - 889: is 65% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region from ORF A, SEQ ID NO 4: amino acids 982 - 1292: is 54% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region from ORF A, SEQ ID NO 4: amino acids 1324 - 1442: is 42% identical to the dehydratase domain of module 4 of the eryA locus of *Saccharopolyspora erythraea*.
Region from ORF A, SEQ ID NO 4: amino acids 1664 - 1840: is 56% identical to the keto-reductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region from ORF A, SEQ ID NO 4: amino acids 1929 - 2000: is 53% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region from ORF A, SEQ ID NO 4: amino acids 2032 - 2453: is 64% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region from ORF A, SEQ ID NO 4: amino acids 2554 - 2865: is 37% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region from ORF A, SEQ ID NO 4: amino acids 2918 - 2991: is 54% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region from ORF A, SEQ ID NO 4: amino acids 3009 - 3431: is 65% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region from ORF A, SEQ ID NO 4: amino acids 3532 - 3847: is 53% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region of ORF A, SEQ ID NO 4: amino acids 4142 - 4307: is 43% identical to the keto-reductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region of ORF A, SEQ ID NO 4: amino acids 4405 - 4490: is 50% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

In addition to these significant homologies with the eryA polyketide synthase of *S. erythraea*, the region of ORF A, SEQ ID NO 4: amino acids 1 - 356 is 53% identical to the postulated starter unit activation domain of the rapamycin polyketide synthase from *Streptomyces hygroscopicus* (Aparicio et al. GENE (1996) **169**, 9-16)

The great similarities found in the amino acid sequence of the enzymatic domains suggest unambiguously that the protein-encoding region (ORF A) of the *A. mediterranai* chromosomal region depicted in SEQ ID NO 3 codes for a typical modular (type 1) polyketide synthase. This very large *A. mediterranei* polyketide synthase encoded by ORF A comprises three complete bioactive modules which are each responsible for condensation of a C2 unit in the macrolide ring of the molecule and correct modification of the initially formed β-keto groups. Because of the homology with activating domains of the rapamycin polyketide synthase, the first module described above very probably comprises an enzymatic domain for activating the aromatic starter unit of rifamycin biosynthesis, 3-amino-5-hydroxybenzoic acid (Ghisalba et al., Biotechnology of Industrial Antibiotics Vandamme E. J. Ed., Decker Inc. New York, (1984) 281-327).

Example 14: Analysis of a second protein encoding region (ORF B) of the cloned *A. mediterranei* chromosomal region depicted in SEQ ID NO 3

The nucleotide sequence in SEQ ID NO 3 is analysed using the Codonpreference computer program (Genetics Computer Group, University of Wisconsin, 1994). This analysis shows that another large open reading frame (ORF B) which codes for a protein is present in the middle region of the sequence (position 15550 - 30759 including stop codon in SEQ ID NO 3). The codons used in ORF B are typical of actinomycetes genes with a high G+C content.

Comparison of the amino acid sequence of ORF B (SEQ ID NO 5, length 5069 amino acids) with other polyketide synthases and specifically with the very well characterized polyketide synthase of *Saccharopolyspora erythraea* (Donadio, Science, (1991) 252, 675-679, DNA sequence gene/EMBL accession N° M63676) gives the following results:

Region of ORF B, SEQ ID NO 5: amino acids 44 - 468: is 62% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 571 - 889: is 56% identical to the acyltransferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 921 - 1055: is 47% identical to the dehydratase domain of module 4 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 1353 - 1525: is 49% identical to the ketoreductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 1621 - 1706: is 53% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 1726 - 2148: is 62% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 2251 - 2560: is 55% identical to the acyltransferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 2961 - 3132: is 49% identical to the ketoreductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 3228 - 3313: is 52% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 3332 - 3755: is 63% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 3857 - 4173: is 52% identical to the acyltransferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 4664 - 4799: is 47% identical to the ketoreductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF B, SEQ ID NO 5: amino acids 4929 - 5014: is 52% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Example 15: Analysis of a third protein-encoding region (ORF C) of the cloned *A. mediterranei* chromosomal region depicted in SEQ ID NO 3

The nucleotide sequence in SEQ ID NO 3 is analysed using the Codonpreference computer program (Genetics Computer Group, University of Wisconsin, 1994). This analysis shows that a large open reading frame (ORF C) which codes for a protein is present in the middle region of the sequence (position 30895 - 36060 including stop codon in SEQ ID NO 3). The codons used in ORF C are typical of actinomycetes genes with a high G+C content.

Comparison of the amino acid sequence of ORF C (SEQ ID NO 6, length 1721 amino acids) with other polyketide synthases and specifically with the very well characterized polyketide synthase from *Saccharopolyspora erythraea* (Donadio, Science, (1991) 252, 675-679, DNA sequence gene/EMBL accession N° M63676) gives the following results:

Region of ORF C, SEQ ID NO 6: amino acids 1 - 414: is 63% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region of ORF C, SEQ ID NO 6: amino acids 514 - 828: is 54% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region of ORF C, SEQ ID NO 6: amino acids 1290 - 1399: is 49% identical to the keto-reductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region of ORF C, SEQ ID NO 6: amino acids 1563 - 1648: is 55% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Example 16: Analysis of a fourth protein-encoding region (ORF D) of the cloned *A. mediterranei* chromosomal region depicted in SEQ ID NO 3

The nucleotide sequence in SEQ ID NO 3 is analysed using the Codonpreference computer program (Genetics Computer Group, University of Wisconsin, 1994). This analysis shows that a large open reading frame (ORF D) which codes for a protein is present in the middle region of the sequence (position 36259 - 41325 including stop codon in SEQ ID NO 3). The codons used in ORF D are typical of actinomycetes genes with a high G+C content.

Comparison of the amino acid sequence of ORF D (SEQ ID NO 7, length 1688 amino acids) with other polyketide synthases and specifically with the very well characterized polyketide synthase from *Saccharopolyspora erythraea* (Donadio, Science, (1991) 252, 675-679, DNA sequence genes/EMBL accession N° M63676) gives the following results:

Region of ORF D, SEQ ID NO 7: amino acids 1 - 418: is 64% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region of ORF D, SEQ ID NO 7: amino acids 524 - 841: is 54% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region of ORF D, SEQ ID NO 7: amino acids 1260 - 1432: is 51% identical to the keto-reductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region of ORF D, SEQ ID NO 7: amino acids 1523 - 1608: is 53% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Example 17: Analysis of a fifth protein-encoding region (ORF E) of the cloned *A. mediterranei* chromosomal region depicted in SEQ ID NO 3

The nucleotide sequence in SEQ ID NO 3 is analysed using the Codonpreference computer program (Genetics Computer Group, University of Wisconsin, 1994). This analysis shows that a large open reading frame (ORF E) which codes for a protein is present in the rear region of the sequence (position 41373 - 51614 including stop codon in SEQ ID NO 3). The codons used in ORF E are typical of actinomycetes genes with a high G+C content.

Comparison of the amino acid sequence of ORF E (SEQ ID NO 8, length 3413 amino acids) with other polyketide synthases and specifically with the very well characterized polyketide synthase from *Saccharopolyspora erythraea* (Donadio, Science, (1991) 252, 675-679, DNA sequence gene/EMBL accession N° M63676) gives the following results:

Region of ORF E, SEQ ID NO 8: amino acids 31 - 451: is 64% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region of ORF E, SEQ ID NO 8: amino acids 555 - 874: is 37% identical to the acyl-transferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region of ORF E, SEQ ID NO 8: amino acids 907 - 1036: is 49% identical to the dehydratase domain of module 4 of the eryA locus of *Saccharopolyspora erythraea*.
Region of ORF E, SEQ ID NO 8: amino acids 1336 - 1500: is 52% identical to the keto-reductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region of ORF E, SEQ ID NO 8: amino acids 1598 - 1683: is 51% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.
Region of ORF E, SEQ ID NO 8: amino acids 1702 - 2124: is 62% identical to the ketoacyl synthase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea*.

Region of ORF E, SEQ ID NO 8: amino acids 2229 - 2543: is 53% identical to the acyltransferase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea.*
Region of ORF E, SEQ ID NO 8: amino acids 2573 - 2700: is 47% identical to the dehydratase domain of module 4 of the eryA locus of *Saccharopolyspora erythraea.*
Region of ORF E, SEQ ID NO 8: amino acids 3054 - 3227: is 52% identical to the ketoreductase domain of module 1 of the eryA locus of *Saccharopolyspora erythraea.*
Region of ORF E, SEQ ID NO 8: amino acids 3324 - 3405: is 51% identical to the acyl carrier protein domain of module 1 of the eryA locus of *Saccharopolyspora erythraea.*

Example 18: Analysis of a sixth protein-encoding region (ORF F) of the cloned *A. mediterranei* chromosomal region depicted in SEQ ID NO 3

The nucleotide sequence in SEQ ID NO 3 is analysed using the Codonpreference computer program (Genetics Computer Group, University of Wisconsin, 1994). This analysis shows that an open reading frame (ORF F) which codes for a protein is present in the rear region of the sequence (position 51713 - 52393 including stop codon in SEQ ID NO 3). The codons used in ORF F are typical of actinomycetes genes with a high G+C content.

Comparison of the amino acid sequence of ORF F (SEQ ID NO 9, length 226 amino acids) with proteins from the EMBL databank (Heidelberg) shows a great similarity with the N-hydroxyarylamine O-acyltransferase from *Salmonella typhimurium* (29% identity over a region of 134 amino acids). There is also significant homology with arylamine acyltransferases from other organisms. It can be concluded from these agreements that the ORF F found in *A. mediterranei* in SEQ ID No 3 codes for an arylamine acyl transferase, and it can be assumed that this enzyme is responsible for the linkage of the long acyl chain produced by the polyketide synthase to the amino group on the starter molecule, 3-amino-5-hydroxybenzoic acid. This reaction would close the rifamycin ring system correctly after completion of the condensation steps by the polyketide synthase.

Example 19: Summarizing assessment of the function of the proteins encoded by ORF A - F in SEQ ID NO 3, and their role in the biosynthesis of rifamycin

The five protein-encoding regions (ORF A-E), described in Examples 13 - 17, of SEQ ID NO 3 comprise proteins with very great similarity (in the amino acid sequence and the arrangement of the enzymatic domains) to polyketide synthases for polyketides of the macrolide type. Taken together, these five multifunctional enzymes comprise 10 polyketide

synthase modules which are each responsible for a condensation step in the polyketide synthesis. 10 such condensation steps are likewise necessary for rifamycin biosynthesis (Ghisalba et al., Biotechnology of Industrial Antibiotics Vandamme E. J. Ed., Decker Inc. New York, (1984) 281-327). The processing of the particular keto groups required by the enzymatic domains within the modules substantially corresponds to the activity required by the rifamycin molecule, if it is assumed that the polyketide synthesis takes place "colinearly" with the arrangement of the modules in the gene cluster of *A. mediterranei* (this is so for other macrolide antibiotics such as erythromycin and rapamycin). It may be added here that it is not certain whether transcription of the five ORFs results in five proteins; in particular, ORF C and ORF D might possibly be translated to a large protein.

An enzymatic domain which is very probably responsible for activating the starter molecule, 3-hydroxy-5-aminobenzoic acid, of rifamycin biosynthesis can be found at the N terminus of ORF A, the start of the polyketide synthase. Directly below the described rifamycin polyketide synthase gene cluster there is a gene (ORF F) which very probably determines a protein which brings about ring closure of the rifamycin molecule after completion of the condensation steps by the polyketide synthase.

It can be concluded on the basis of these findings that the *A. mediterranei* chromosomal region described in SEQ ID NO 3 is responsible for the ten condensation steps required for rifamycin polyketide synthesis, including activation of the starter molecule 3-hydroxy-5-aminobenzoic acid, and the concluding ring closure.

<u>Deposited microorganisms</u>

The following microorganisms and plasmids have been deposited at the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM), Mascheroder Weg 1b, D-38124 Braunschweig, in accordance with the requirements of the Budapest Treaty.

Microorganism/Plasmid	Date of deposit	Deposit number
E. coli with plasmid pRi7-3	10.08.96	DSM 11114
E. coli with plasmid pNE112	14.07.97	DSM 11657
E. coli with plasmid pNE95	14.07.97	DSM 11656
E. coli with plasmid pRi44-2	14.07.97	DSM 11655

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: Novartis AG

(B) STREET: Schwarzwaldallee 215

(C) CITY: Basel

(E) COUNTRY: Switzerland

(F) POSTAL CODE (ZIP): 4058

(G) TELEPHONE: +41 61 324 1111

(H) TELEFAX: + 41 61 322 75 32

(ii) TITLE OF INVENTION: Rifamycin biosynthesis gene cluster

(iii) NUMBER OF SEQUENCES: 9

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk

(B) COMPUTER: IBM PC compatible

(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

GGTACCCGGT GTTCGCGACG GCGTTCGACG AGGCTTGCGA GCAGCTGGAC GTCTGTCTGG 60

CCGGCCGTGC CGGGCACCGC GTGCGGGACG TCGTGCTCGG CGAAGTGCCC GCCGAAACCG 120

GGCTGCTGAA CCAGACGGTC TTCACCCAAG CCGGGCTGTT CGCGGTGGAG AGCGCGCTGT 180

TCCGGCTCGC CGAATCCTGG GGTGTCCGGC CGGACGTGGT GCTCGGCCAC TCCATCGGGG 240

AGATCACCGC CGCGTATGCC GCGGGCGTCT TCTCGCTGCC GGACGCCGCC CGGATCGTCG 300

CGGCGCGCGG CCGGCTGATG CAGGCGCTGG CGCCGGGCGG GGCGATGGTC GCCGTCGCCG 360

CCTCCGAAGC CGAGGTGGCC GAACTGCTCG GCGACGGCGT GGAACTCGCC GCCGTCAACG 420

GCCCTTCGGC GGTAGTCCTT TCCGGGGACG CGGACGCGGT CGTCGCGGCC GCCGCCCGCA 480

TGCGCGAGCG CGGGCACAAG ACCAAGCAGC TCAAGGTTTC GCACGCGTTC CACTCCGCGC 540

GGATGGCGCC GATGCTGGCG GAGTTCGCCG CCGAGCTGGC CGGCGTGACG TGGCGCGAGC 600

CGGAGATCCC GGTGGTCTCC AACGTGACCG GCCGGTTCGC CGAGCCCGGC GAACTGACCG 660

AGCCGGGCTA CTGGGCCGAG CACGTGCGGC GGCCGGTGCG GTTCGCCGAG GGCGTCGCGG 720

CCGCGACGGA GTCCGGCGGC TCGCTGTTCG TGGAGCTCGG GCCGGGGGCG GCGCTGACCG 780

CCCTCGTCGA GGAGACGGCC GAGGTCACCT GCGTCGCGGC CCTGCGGGAC GACCGCCCGG 840

AGGTCACCGC GCTGATCACC GCGGTCGCCG AGCTGTTCGT CCGCGGGGTT GCGGTCGATT 900

GGCCGGCCCT GCTGCCGCCG GTCACCGGGT TCGTCGACCT GCCGAAGTAC GCCTTCGACC 960

AGCAGCACTA TTGGCTGCAG CCCGCCGCGC AGGCCACGGA CGCGGCCTCG CTCGGGCAGG 1020

TCGCGGCCGA CCACCCGCTG CTGGGCGCGG TGGTCCGGCT GCCGCAGTCG GACGGCCTGG 1080

TCTTCACCTC GCGGCTGTCA TTGAAATCGC ACCCGTGGCT GGCCGACCAC GTCATCGGCG 1140

GGGTGGTGCT CGTCGCGGGC ACCGGGCTCG TCGAGCTGGC CGTCCGGGCC GGGGACGAGG 1200

CCGGCTGCCC GGTCCTCGAA GAACTCGTCA TCGAGGCTCC GCTGGTCGTC CCCGACCACG 1260

GCGGGGTCCG GATCCAGGTC GTCGTGGGGG CACCGGGGGA GACCGGTTCG CGCGCGGTCG 1320

AGGTGTACTC CCTGCGCGAG GACGCCGGTG CCGAAGTGTG GGCCCGGCAC GCCACCGGGT 1380

TCCTGGCTGC GACGCCGTCG CAGCACAAGC CGTTCGACTT CACCGCCTGG CCGCCGCCCG 1440

GCGTCGAGCG CGTCGACGTC GAGGACTTCT ACGACGGCTT CGTCGACCGC GGGTACGCCT 1500

ACGGGCCGTC GTTCCGGGGC CTGCGGGCGG TGTGGCGGCG CGGCGACGAA GTGTTCGCCG 1560

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GGCCGGTGCT GCCGTTCGCC TGGAACGGCC TGGTGCTGCA CGCGGCCGGG GCGTCCGCGC 1740

TGCGGGTCCG GCTCGCCCCG AGCGGTCCGG ACGCCCTGTC GGTCGAGGCC GCGGACGAGG 1800

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TGGGCGCGGC GGCGAACCAC GACGCGTTGT TCCGCGTGGA GTGGACCGAG ATTTCCTCGG 1920

CTGGAGACGT TCCGGCGGAC CACGTCGAAG TGCTCGAAGC CGTCGGCGAG GATCCCCTGG 1980

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CGGTGTGGGG CCTGATCCGG GCCGCGCAGG CGGAAAACCC GGACCGGATC GTGCTGCTGG 2160

ACACCGACGG TGAAGTGCCG CTAGGCCGGG TGCTGGCCAC CGGCGAGCCC CAAACAGCCG 2220

TCCGAGGCGC CACGCTGTTC GCCCCGCGGC TGGCCCGCGC CGAGGCCGCG GAGGCACCGG 2280

CAGTGACCGG CGGGACGGTC CTGATCTCGG GCGCCGGCTC GCTGGGCGCG CTCACCGCCC 2340

GGCACCTGGT CGCCCGGCAC GGAGTCCGGC GGCTGGTGCT CGTCAGCCGC CGTGGCCCCG 2400

ACGCCGACGG CATGGCCGAA CTGACCGCTG AACTCATCGC TCAGGGCGCC GAGGTCGCCG 2460

TAGTCGCTTG CGACCTGGCC GACCGGGACC AGGTCCGGGT ACTGCTGGCC GAGCACCGCC 2520

CGAACGCCGT CGTGCACACG GCCGGTGTTC TCGACGACGG CGTCTTCGAG TCGCTGACGC 2580

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TGACCCGCGA ACTGGATCTT CGCGCGTTCG TCGTGTTCTC CTCCGCCTCC GGGGTCTTCG 2700

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ACCGCCGGGC CGCGGGCCTG CCCGGCACAT CGCTGGCCTG GGGCCTGTGG GAACAGACCG 2820

ACGGGATGAC CGCGCACCTC GGCGACGCCG ACCAGGCGCG GGCGAGTCGC GGCGGGGTCC 2880

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TCCCGGTCAA GCTGGACCTG CGCAAGACCC GCGCCGGCGG GACGGTGCCG CACCTGCTGC 3000

GCGGCCTGGT CCGCCCGGGA CGGCAGCAGG CCCGTCCGGC GTCCACTGTG GACAACGGAC 3060

TGGCCGGGCG ACTCGCCGGG CTCGCGCCGG CGGAGCAGGA GGCGCTGCTG CTCGACGTCG 3120

TCCGCACGCA GGTCGCGCTG GTGCTCGGGC ACGCCGGGCC GGAGGCCGTC CGCGCGGACA 3180

CGGCGTTCAA GGACACCGGC TTCGACTCGC TGACGTCGGT GGAACTGCGC AACCGGCTGC 3240

GCGAGGCGAG CGGGCTGAAG CTGCCCGCGA CGCTCGTCTT CGACTACCCG ACGCCGGTCG 3300

CGCTGGCCCG CTACCTGCGT GACGAATTCG GCGACACGGT GGCAACAACT CCGGTGGCCA 3360

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AGGGCGCCGA CGTCGGGGTG TTCGCCGGGG TGTCCAACCA GGGCTATGGG ATGGGCGCGG 3780

ATCCGGCCGA ACTGGCGGGG TACGCGAGCA CGGCGGGCGC TTCGAGCGTC GTCTCGGGCC 3840

GAGTCTCGTA CGTCTTCGGG TTCGAAGGAC CGGCGGTCAC GATCGACACG GCTTGCTCGT 3900

CGTCGCTGGT GGCGATGCAC CTGGCCGGGC AGGCGCTGCG GCAGGGCGAG TGCTCGATGG 3960

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GCTGGGCCGA GGGCGTCGGG GTCGTCGTGC TGGAGCGGCT GTCGGTGGCG CGCGAGCGCG 4140

GGCACCGGGT GCTGGCCGTG CTGCGCGGCA GCGCGGTCAA CTCCGACGGC GCGTCCAACG 4200

GCCTGACCGC CCCCAACGGG CCGTCGCAGC AACGGGTGAT CCGCCGGGCC CTGGCCGGCG 4260

CCGGCCTCGA ACCGTCCGAT GTGGACATCG TGGAAGGGCA CGGCACCGGG ACGGCGCTGG 4320

GCGACCCGAT CGAGGCGCAG GCCCTGCTGG CCACCTACGG CAAGGACCGC GACCCGGAGA 4380

CGCCGTTGTG GCTGGGGTCG GTGAAGTCGA ACTTCGGCCA CACGCAGTCC GCGGCCGGCG 4440

TGGCCGGGGT GATCAAGATG GTGCAGGCGC TGCGCCACGG CGTCATGCCG CCCACCCTGC 4500

ACGTGGACCG GCCCACCAGC CAGGTCGACT GGTCCGCGGG GGCCGTCGAA GTGCTGACCG 4560

AGGCACGGGA GTGGCCGCGG AACGGCCGTC CGCGCCGGGC CGGGGTGTCC TCGTTCGGGA 4620

TCAGCGGCAC GAACGCCCAC CTGATCATCG AAGAAGCACC GGCCGAGCCA CAGCTTGCCG 4680

GACCACCGCC GGACGGCGGT GTGGTGCCGC TGGTCGTCTC GGCTCGCAGC CCCGGTGCCC 4740

TGGCCGGTCA GGCGCGTCGG CTGGCCACGT TCCTCGGCGA CGGGCCCCTT TCCGACGTCG 4800

CCGGTGCGCT GACGAGCCGC GCCCTGTTCG GCGAGCGCGC GGTCGTCGTG GCGGATTCGG 4860

CCGAGGAAGC CCGCGCCGGT CTGGGCGCAC TGGCCCGCGG CGAAGACGCG CCGGGCCTGG 4920

TCCGCGGCCG GGTGCCCGCG TCCGGCCTGC CGGGCAAGCT CGTGTGGGTG TTCCCCGGGC 4980

AGGGGACGCA GTGGGTGGGC ATGGGCCGCG AACTCCTCGA AGAGTCTCCG GTGTTCGCCG 5040

AGCGGATCGC CGAGTGTGCG GCCGCGCTGG AGCCGTGGAT CGGCTGGTCG CTGTTCGACG 5100

TCCTCCGTGG CGACGGTGAC CTCGATCGGG TCGATGTGCT GCAGCCCGCG TGCTTTGCGG 5160

TGATGGTCGG CTTGGCCGCG GTGTGGTCCT CGGCCGGGGT GGTCCCCGAT GCGGTGCTCG 5220

GCCACTCCCA GGGTGAGATC GCCGCGGCGT GCGTGTCGGG TGCGTTGTCG CTGGAGGATG 5280

CGGCGAAGGT GGTTGCCCTG CGCAGCCAGG CCATCGCCGC GAAGCTCTCC GGCCGCGGCG 5340

GGATGGCTTC GGTCGCCTTG GGCGAAGCCG ATGTGGTGTC GCGGCTGGCG GACGGGGTCG 5400

AGGTGGCTGC CGTCAACGGT CCGGCGTCCG TGGTGATCGC GGGGGATGCC CAGGCCCTCG 5460

ACGAAACGCT GGAAGCGCTG TCCGGTGCGG GAATCCGGGC TCGGCGGGTG GCGGTGGACT 5520

ACGCCTCGCA CACCCGGCAC GTCGAAGACA TCGAAGACAC CCTCGCCGAA GCGCTGGCCG 5580

GGATCGACGC CCGGGCGCCG CTGGTGCCGT TCCTCTCCAC CCTCACCGGC GAGTGGATCC 5640

GGGACGAGGG CGTCGTGGAC GGCGGCTACT GGTACC 5676

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1891 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Tyr Pro Val Phe Ala Thr Ala Phe Asp Glu Ala Cys Glu Gln Leu Asp
1 5 10 15

Val Cys Leu Ala Gly Arg Ala Gly His Arg Val Arg Asp Val Val Leu
20 25 30

Gly Glu Val Pro Ala Glu Thr Gly Leu Leu Asn Gln Thr Val Phe Thr
35 40 45

Gln Ala Gly Leu Phe Ala Val Glu Ser Ala Leu Phe Arg Leu Ala Glu
50 55 60

Ser Trp Gly Val Arg Pro Asp Val Val Leu Gly His Ser Ile Gly Glu
65 70 75 80

Ile Thr Ala Ala Tyr Ala Ala Gly Val Phe Ser Leu Pro Asp Ala Ala
85 90 95

Arg Ile Val Ala Ala Arg Gly Arg Leu Met Gln Ala Leu Ala Pro Gly
100 105 110

Gly Ala Met Val Ala Val Ala Ala Ser Glu Ala Glu Val Ala Glu Leu
115 120 125

Leu Gly Asp Gly Val Glu Leu Ala Ala Val Asn Gly Pro Ser Ala Val
130 135 140

Val Leu Ser Gly Asp Ala Asp Ala Val Val Ala Ala Ala Ala Arg Met
145 150 155 160

Arg Glu Arg Gly His Lys Thr Lys Gln Leu Lys Val Ser His Ala Phe
165 170 175

His Ser Ala Arg Met Ala Pro Met Leu Ala Glu Phe Ala Ala Glu Leu
180 185 190

Ala Gly Val Thr Trp Arg Glu Pro Glu Ile Pro Val Val Ser Asn Val
195 200 205

Thr Gly Arg Phe Ala Glu Pro Gly Glu Leu Thr Glu Pro Gly Tyr Trp
210 215 220

Ala Glu His Val Arg Arg Pro Val Arg Phe Ala Glu Gly Val Ala Ala
225 230 235 240

Ala Thr Glu Ser Gly Gly Ser Leu Phe Val Glu Leu Gly Pro Gly Ala
245 250 255

Ala Leu Thr Ala Leu Val Glu Glu Thr Ala Glu Val Thr Cys Val Ala
260 265 270

Ala Leu Arg Asp Asp Arg Pro Glu Val Thr Ala Leu Ile Thr Ala Val
275 280 285

Ala Glu Leu Phe Val Arg Gly Val Ala Val Asp Trp Pro Ala Leu Leu
290 295 300

Pro Pro Val Thr Gly Phe Val Asp Leu Pro Lys Tyr Ala Phe Asp Gln
305 310 315 320

Gln His Tyr Trp Leu Gln Pro Ala Ala Gln Ala Thr Asp Ala Ala Ser
325 330 335

Leu Gly Gln Val Ala Ala Asp His Pro Leu Leu Gly Ala Val Val Arg
340 345 350

Leu Pro Gln Ser Asp Gly Leu Val Phe Thr Ser Arg Leu Ser Leu Lys
355 360 365

Ser His Pro Trp Leu Ala Asp His Val Ile Gly Gly Val Val Leu Val
370 375 380

Ala Gly Thr Gly Leu Val Glu Leu Ala Val Arg Ala Gly Asp Glu Ala
385 390 395 400

Gly Cys Pro Val Leu Glu Glu Leu Val Ile Glu Ala Pro Leu Val Val
405 410 415

Pro Asp His Gly Gly Val Arg Ile Gln Val Val Val Gly Ala Pro Gly
420 425 430

Glu Thr Gly Ser Arg Ala Val Glu Val Tyr Ser Leu Arg Glu Asp Ala
435 440 445

Gly Ala Glu Val Trp Ala Arg His Ala Thr Gly Phe Leu Ala Ala Thr
450 455 460

Pro Ser Gln His Lys Pro Phe Asp Phe Thr Ala Trp Pro Pro Pro Gly

465 470 475 480

Val Glu Arg Val Asp Val Glu Asp Phe Tyr Asp Gly Phe Val Asp Arg
485 490 495

Gly Tyr Ala Tyr Gly Pro Ser Phe Arg Gly Leu Arg Ala Val Trp Arg
500 505 510

Arg Gly Asp Glu Val Phe Ala Glu Val Ala Leu Ala Glu Asp Asp Arg
515 520 525

Ala Asp Ala Ala Arg Phe Gly Ile His Pro Gly Leu Leu Asp Ala Ala
530 535 540

Leu His Ala Gly Met Ala Gly Ala Thr Thr Thr Glu Glu Pro Gly Arg
545 550 555 560

Pro Val Leu Pro Phe Ala Trp Asn Gly Leu Val Leu His Ala Ala Gly
565 570 575

Ala Ser Ala Leu Arg Val Arg Leu Ala Pro Ser Gly Pro Asp Ala Leu
580 585 590

Ser Val Glu Ala Ala Asp Glu Ala Gly Gly Leu Val Val Thr Ala Asp
595 600 605

Ser Leu Val Ser Arg Pro Val Ser Ala Glu Gln Leu Gly Ala Ala Ala
610 615 620

Asn His Asp Ala Leu Phe Arg Val Glu Trp Thr Glu Ile Ser Ser Ala
625 630 635 640

Gly Asp Val Pro Ala Asp His Val Glu Val Leu Glu Ala Val Gly Glu
645 650 655

Asp Pro Leu Glu Leu Thr Gly Arg Val Leu Glu Ala Val Gln Thr Trp
660 665 670

Leu Ala Asp Ala Ala Asp Asp Ala Arg Leu Val Val Val Thr Arg Gly
675 680 685

Ala Val His Glu Val Thr Asp Pro Ala Gly Ala Ala Val Trp Gly Leu
690 695 700

Ile Arg Ala Ala Gln Ala Glu Asn Pro Asp Arg Ile Val Leu Leu Asp
705 710 715 720

Thr Asp Gly Glu Val Pro Leu Gly Arg Val Leu Ala Thr Gly Glu Pro
725 730 735

Gln Thr Ala Val Arg Gly Ala Thr Leu Phe Ala Pro Arg Leu Ala Arg
740 745 750

Ala Glu Ala Ala Glu Ala Pro Ala Val Thr Gly Gly Thr Val Leu Ile
755 760 765

Ser Gly Ala Gly Ser Leu Gly Ala Leu Thr Ala Arg His Leu Val Ala
770 775 780

Arg His Gly Val Arg Arg Leu Val Leu Val Ser Arg Arg Gly Pro Asp
785 790 795 800

Ala Asp Gly Met Ala Glu Leu Thr Ala Glu Leu Ile Ala Gln Gly Ala
805 810 815

Glu Val Ala Val Val Ala Cys Asp Leu Ala Asp Arg Asp Gln Val Arg
820 825 830

Val Leu Leu Ala Glu His Arg Pro Asn Ala Val Val His Thr Ala Gly
835 840 845

Val Leu Asp Asp Gly Val Phe Glu Ser Leu Thr Arg Glu Arg Leu Ala
850 855 860

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Lys Val Phe Ala Pro Lys Val Thr Ala Ala Asn His Leu Asp Glu Leu
865                 870                 875                 880

Thr Arg Glu Leu Asp Leu Arg Ala Phe Val Val Phe Ser Ser Ala Ser
                885                 890                 895

Gly Val Phe Gly Ser Ala Gly Gln Gly Asn Tyr Ala Ala Ala Asn Ala
            900                 905                 910

Tyr Leu Asp Ala Val Val Ala Asn Arg Arg Ala Ala Gly Leu Pro Gly
        915                 920                 925

Thr Ser Leu Ala Trp Gly Leu Trp Glu Gln Thr Asp Gly Met Thr Ala
    930                 935                 940

His Leu Gly Asp Ala Asp Gln Ala Arg Ala Ser Arg Gly Gly Val Leu
945                 950                 955                 960

Ala Ile Ser Pro Ala Glu Gly Met Glu Leu Phe Asp Ala Ala Pro Asp
                965                 970                 975

Gly Leu Val Val Pro Val Lys Leu Asp Leu Arg Lys Thr Arg Ala Gly
            980                 985                 990

Gly Thr Val Pro His Leu Leu Arg Gly Leu Val Arg Pro Gly Arg Gln
        995                 1000                1005

Gln Ala Arg Pro Ala Ser Thr Val Asp Asn Gly Leu Ala Gly Arg Leu
    1010                1015                1020

Ala Gly Leu Ala Pro Ala Glu Gln Glu Ala Leu Leu Leu Asp Val Val
1025                1030                1035                1040

Arg Thr Gln Val Ala Leu Val Leu Gly His Ala Gly Pro Glu Ala Val
                1045                1050                1055

Arg Ala Asp Thr Ala Phe Lys Asp Thr Gly Phe Asp Ser Leu Thr Ser
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1060 1065 1070

Val Glu Leu Arg Asn Arg Leu Arg Glu Ala Ser Gly Leu Lys Leu Pro
1075 1080 1085

Ala Thr Leu Val Phe Asp Tyr Pro Thr Pro Val Ala Leu Ala Arg Tyr
1090 1095 1100

Leu Arg Asp Glu Phe Gly Asp Thr Val Ala Thr Thr Pro Val Ala Thr
1105 1110 1115 1120

Ala Ala Ala Ala Asp Ala Gly Glu Pro Ile Ala Ile Val Gly Met Ala
1125 1130 1135

Cys Arg Leu Pro Gly Gly Val Thr Asp Pro Glu Gly Leu Trp Arg Leu
1140 1145 1150

Val Arg Asp Gly Leu Glu Gly Leu Ser Pro Phe Pro Glu Asp Arg Gly
1155 1160 1165

Trp Asp Leu Glu Asn Leu Phe Asp Asp Asp Pro Asp Arg Ser Gly Thr
1170 1175 1180

Thr Tyr Thr Ser Arg Gly Gly Phe Leu Asp Gly Ala Gly Leu Phe Asp
1185 1190 1195 1200

Ala Gly Phe Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro
1205 1210 1215

Gln Gln Arg Leu Leu Leu Glu Ala Ala Trp Glu Ala Leu Glu Gly Thr
1220 1225 1230

Gly Val Asp Pro Gly Ser Leu Lys Gly Ala Asp Val Gly Val Phe Ala
1235 1240 1245

Gly Val Ser Asn Gln Gly Tyr Gly Met Gly Ala Asp Pro Ala Glu Leu
1250 1255 1260

Ala Gly Tyr Ala Ser Thr Ala Gly Ala Ser Ser Val Val Ser Gly Arg
1265 1270 1275 1280

Val Ser Tyr Val Phe Gly Phe Glu Gly Pro Ala Val Thr Ile Asp Thr
1285 1290 1295

Ala Cys Ser Ser Ser Leu Val Ala Met His Leu Ala Gly Gln Ala Leu
1300 1305 1310

Arg Gln Gly Glu Cys Ser Met Ala Leu Ala Gly Gly Val Thr Val Met
1315 1320 1325

Gly Thr Pro Gly Thr Phe Val Glu Phe Ala Lys Gln Arg Gly Leu Ala
1330 1335 1340

Gly Asp Gly Arg Cys Lys Ala Tyr Ala Glu Gly Ala Asp Gly Thr Gly
1345 1350 1355 1360

Trp Ala Glu Gly Val Gly Val Val Val Leu Glu Arg Leu Ser Val Ala
1365 1370 1375

Arg Glu Arg Gly His Arg Val Leu Ala Val Leu Arg Gly Ser Ala Val
1380 1385 1390

Asn Ser Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser
1395 1400 1405

Gln Gln Arg Val Ile Arg Arg Ala Leu Ala Gly Ala Gly Leu Glu Pro
1410 1415 1420

Ser Asp Val Asp Ile Val Glu Gly His Gly Thr Gly Thr Ala Leu Gly
1425 1430 1435 1440

Asp Pro Ile Glu Ala Gln Ala Leu Leu Ala Thr Tyr Gly Lys Asp Arg
1445 1450 1455

Asp Pro Glu Thr Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Phe Gly
1460 1465 1470

His Thr Gln Ser Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Gln
1475 1480 1485

Ala Leu Arg His Gly Val Met Pro Pro Thr Leu His Val Asp Arg Pro
1490 1495 1500

Thr Ser Gln Val Asp Trp Ser Ala Gly Ala Val Glu Val Leu Thr Glu
1505 1510 1515 1520

Ala Arg Glu Trp Pro Arg Asn Gly Arg Pro Arg Arg Ala Gly Val Ser
1525 1530 1535

Ser Phe Gly Ile Ser Gly Thr Asn Ala His Leu Ile Ile Glu Glu Ala
1540 1545 1550

Pro Ala Glu Pro Gln Leu Ala Gly Pro Pro Pro Asp Gly Gly Val Val
1555 1560 1565

Pro Leu Val Val Ser Ala Arg Ser Pro Gly Ala Leu Ala Gly Gln Ala
1570 1575 1580

Arg Arg Leu Ala Thr Phe Leu Gly Asp Gly Pro Leu Ser Asp Val Ala
1585 1590 1595 1600

Gly Ala Leu Thr Ser Arg Ala Leu Phe Gly Glu Arg Ala Val Val Val
1605 1610 1615

Ala Asp Ser Ala Glu Glu Ala Arg Ala Gly Leu Gly Ala Leu Ala Arg
1620 1625 1630

Gly Glu Asp Ala Pro Gly Leu Val Arg Gly Arg Val Pro Ala Ser Gly
1635 1640 1645

Leu Pro Gly Lys Leu Val Trp Val Phe Pro Gly Gln Gly Thr Gln Trp

1650 1655 1660

Val Gly Met Gly Arg Glu Leu Leu Glu Glu Ser Pro Val Phe Ala Glu
1665 1670 1675 1680

Arg Ile Ala Glu Cys Ala Ala Ala Leu Glu Pro Trp Ile Gly Trp Ser
1685 1690 1695

Leu Phe Asp Val Leu Arg Gly Asp Gly Asp Leu Asp Arg Val Asp Val
1700 1705 1710

Leu Gln Pro Ala Cys Phe Ala Val Met Val Gly Leu Ala Ala Val Trp
1715 1720 1725

Ser Ser Ala Gly Val Val Pro Asp Ala Val Leu Gly His Ser Gln Gly
1730 1735 1740

Glu Ile Ala Ala Ala Cys Val Ser Gly Ala Leu Ser Leu Glu Asp Ala
1745 1750 1755 1760

Ala Lys Val Val Ala Leu Arg Ser Gln Ala Ile Ala Ala Lys Leu Ser
1765 1770 1775

Gly Arg Gly Gly Met Ala Ser Val Ala Leu Gly Glu Ala Asp Val Val
1780 1785 1790

Ser Arg Leu Ala Asp Gly Val Glu Val Ala Ala Val Asn Gly Pro Ala
1795 1800 1805

Ser Val Val Ile Ala Gly Asp Ala Gln Ala Leu Asp Glu Thr Leu Glu
1810 1815 1820

Ala Leu Ser Gly Ala Gly Ile Arg Ala Arg Arg Val Ala Val Asp Tyr
1825 1830 1835 1840

Ala Ser His Thr Arg His Val Glu Asp Ile Glu Asp Thr Leu Ala Glu
1845 1850 1855

Ala Leu Ala Gly Ile Asp Ala Arg Ala Pro Leu Val Pro Phe Leu Ser
1860 1865 1870

Thr Leu Thr Gly Glu Trp Ile Arg Asp Glu Gly Val Val Asp Gly Gly
1875 1880 1885

Tyr Trp Tyr
1890

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 53789 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

GAATTCCAGG CCGTCGACGG CTGCGACATC GCGGTCTTCC GGTGGTCGCA CCGCACGAAG 60

ATCGCCGAAT AAGAATTTCC GGATCTCCCA CGGGAAAGGT TTCCATGACC GACGCAATAT 120

CCTTCGAGGT GCCGTGGGAC CGGACCGACA AGTTCGACCC GCCCGCGGTG TTCGACTCTC 180

TGCGCGAAGA ACGTCCGCTC GCGAAGATGG TTTACCCGGA TGGGCACGTC GGCTGGATCG 240

TTTCCAGCTA CGAGCTGGTC CGCGAGGTCC TCAGCGACCT GCGGTTCAGC CACAGCTGCG 300

AAGTCGGCCA CTTCCCGGTG ACCCACCAGG GCCAGGTCAT CCCGACCCAC CCGCTGATCC 360

CCGGCATGTT CATCCACATG GACCCGCCCG AGCACACGCG CTACCGCAAG CTGCTGACCG 420

GCGAGTTCAC CGTCCGCCGC GCCAGCAGGC TGATCCCGCG GGCCGAGGCC GTGGCCGCCG 480

AGCAGATCGA GGTCATGCGG GCCAAGGGCG CCCCCGCGGA CGTGGTCATG GACTTCGCCA 540

AGCCGCTGGT GCTGCGGATG CTGGGCGAGC TCGTCGGCCT GCCCTACGAG GAACGCGACC 600

GGTACGTGCC CGCGGTGACC CTCCTGCACG ACGCCGAAGC GGACCCGGCC GAGGCCGCGG 660

CCGCCTACGA GGTGGCCGGG AAGTTCTTCG ACGAGGTCAT CGAGCGCCGC CGGCAGCGGC 720

CCCAGGACGA CCTCATCAGC TCGCTCGTCA CCGAGGACCT GACCCAGGAG GAGCTGCGCA 780

ACATCGTCAC CCTGCTGCTG TTCGCCGGGT ACGAGACCAC CGAGGGCGCG CTCGCCACCG 840

GCGTCTTCGC GCTGCTGCAC CACACCGATC AGCTGGCGGC ACTGCGCGCG GAGCCGGAAA 900

AGCTCGACGC CGCGATCGAA GAGCTGCTGC GCTACCTGAC CGTCAACCAG TACCACACCT 960

ACCGCACCGC GCTGGAGGAC GTGAAGCTGG AGGGCGAGCT GATCAAGAAG GGCGACACGG 1020

TGACGGTGTC GCTGCCCGCG GCCAACCGCG ACCCGGCCAA GTTCGGCTGT CCCGCGGAGC 1080

TCGACATCGA GCGGGACACC TCCGGCCACG TCGCGTTCGG CTTCGGCATC CACCAGTGCC 1140

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TCCCCGAGCT CCGGCTGGCC GTCCCGGCCG ACGAGGTTCC GCTGCGGCTG AAGGGTTCCG 1260

TCTTCTCGGT GAAGAAGCTG CCCGTCTCCT GGTGAGCGTT CTTCCCCTCG AACACCCGAA 1320

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GGCGACCTCG AGGCGCGGAC GCGCCGGCTG GCCGGGCACC TGGCCGGCCT CGGTGTCCGG 1500

CACGGCGACC GGGTGGCGAT CTGCCTCGGC AACCGGGTGT CCACTGTGGA GAGTTACTTC 1560

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GGCGTCGTGT CCACGCAGCG CAACTGCCTC TGGTCCGTCG CTTCCTGCTA CGTGCCGTTC 1920

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GCCAACGCCG AGCTGGATGC GTTGGCGCGC CAGCGGAACA GCCTCGACCT GCCCGCGGTG 7320

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GACCTGCGGC GCAACCAGCG GATCGGCATG TCCGGGCTTC CCGCCGACGA GGGCATGGCG 7440

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AACGAGGCGC TCGCCATGGA CCCGCAGCAG CGGCTGCTGC TGGAGACGTC CTGGGAGCTG 8220

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CCCGTGCGGC GTCCACTGTG GAGGAGAACT GGGCCGGCCG GCTGGCCGGG CTCGAGCCGG 51360

CCGAGCGGGG CCAGGTCCTC CTGGAACTGG TGCGCGCCCA GGTGGCAGGG GTCCTGGGCT 51420

ACCGCGCCGC CCACCAGGTC GACCCGGACC AGGGCCTGTT CGAGATCGGG TTCGACTCGC 51480

TCACCGCGAT CGAACTCCGC AACCGGCTGC GCGCCAGGAC CGAACGGAAG ATCTCGCCCG 51540

GTGTCGTCTT CGACCATCCC ACGCCGGCCC TGCTCGCCGC GCACTTGAAC GAGCTGCTCC 51600

GAAAGAAGGT GTGAACGTGT TCGACGTGGA GACCTACCTC CAGCGGATCG GCTGCGGCGG 51660

GGAAACCGGC GTGGACCTCG AAACGCTGGC GAAGCTGCAG AAGAGCCACC TGATGGCGAT 51720

CCCGTACAGC AGCCTCGCCT ACGAACTCCG GGACGCGGTG AACGTCGTCG ACCTCGACGA 51780

GGACGACGTC TTCGTCACCA GCATCGCCGA AGGGCAGGGC GGCGCCTGCT ACCACCTGAA 51840

CCGGCTGTTC CACCGGCTCC TGACCGAACT CGGCTACGAC GTCACGCCGC TGGCCGGCAG 51900

CACCGCCGAA GGCCGGGAGA CCTTCGGCAC CGACGTCGAG CACATGTTCA ACCTGGTCAC 51960

CCTGGACGGC GCCGACTGGC TCGTGGACGT CGGCTACCCC GGCCCCACCT ACGTCGAGCC 52020

ACTGGCGGTC TCGCCCGCGG TGCAGACCCA GTACGGGAGC CAGTTCCGGT TGGTGGAACA 52080

GGAAACCGGT TATGCGCTGC AACGCCGGGG TGCGGTCACC CGCTGGAGCG TCGTCTACAC 52140

GTTCACGACG CAACCGCGTC AGTGGAGTGA CTGGAAGGAA CTGGAGGACA ACTTCCGGGC 52200

CCTCGTGGGG GACACCACCC GCACCGACAC GCAGGAAACC CTGTGCGGCC GCGCGTTCGC 52260

GAACGGCCAG GTCTTCCTGC GGCAGCGCCG CTACCTGACG GTCGAGAACG GCCGCGAGCA 52320

GGTGCGCACG ATCACCGACG ACGACGAGTT CCGGGCGCTG GTGTCCCGCG TGCTGTCCGG 52380

CGACCACGGC TGAACTGGCG AAAGGCACGA CGATGACGGA AAAAGCGGGC CTGCTGGCGA 52440

AGTTCGCCGG CCTCTGCAAA ACCGCCTACG AGCACCACTA CATCCCGTAC CTGCACTTCT 52500

TCTACGGCGG CGAGTACCTC CACCACGGCA GCGAGCCGGT GTCCCGGATC GCGGACCTGC 52560

CGTACGTGAC CGTGCCGGAG CCGCGGAAGA AGGCGCCGTG AGGACGACGA TCCCGGTCCG 52620

CCTGGCGGAA CGGTCCTACG ACGTGCTCGT CGGCCCCGGG GTGCGGGCGG CGCTGCCCGA 52680

GGTCGTCCGG CGGCTCGGCG CGAGACGGGC CGTGGTCGTG TCGGCCCGGC CGGCGGACTG 52740

GGTGCCCGGC ACCGGCGTCG AGACCCTGCT GCTCCAGGCG CGCGACGGCG AGCCGACCAA 52800

GCGGCTGTCC ACAGTGGAGG AACTGTGCGG TGAGTTCGCG CGGTTCGGGC TCACCCGGTC 52860

CGACGTCGTG GTCTCCTGCG GCGGCGGCAC GACCACGGAC GTCGTCGGGC TCGCGGCCGC 52920

GCTGTACCAC CGGGGGGTCG CCGTGGTCCA CCTGCCCACG TCCCTGCTCG CCCAGGTCGA 52980

CGCCAGCGTC GGCGGGAAGA CCGCGGTGAA CCTGCCGGCG GGCAAGAACC TCGTCGGGGC 53040

GTACTGGCAG CCCAGCGCGG TGCTGTGCGA CACGGACTAC CTGACGACGC TGCCGCGGCG 53100

GGAGGTGCTG AACGGCCTCG GCGAGATCGC CCGCTGCCAC TTCATCGGCG CGCCGGACCT 53160

GCGGGGGCGC TCGCGCCCGG AGCAGATCGC CGCCAGCGTC ACCCTCAAGG CGGGCATCGT 53220

CGCGCAGGAC GAGCGGGACA CCGGCCCGCG GCACCTGCTC AACTACGGCC ACACGCTGGG 53280

GCACGCGCTG GAGATCGCGA CCGGCTTCGC CCTGCGCCAC GGCGAGGCGG TGGCGATCGG 53340

CACGGTCTTC GCGGGCCGGC TGGCCGGCGC GCTCGGCCGC CTCGACCAGT CCGGTGTGGA 53400

CGAACACCTC GCCGTCGTCC GCCACTACGG CCTGCCCGCC GCGCTGCCCG CGGACGTCGA 53460

CCCGGCGGTG CTCGTCCGGC AGATGTACCG GGACAAGAAG GCGATCACCG GGCTCGCCTT 53520

CGTCCTGGCC GGGCCGCGGG GCGCGGAGCT GGTGAGCGAC GTGCCGGCGC CGGTCGTCAC 53580

CGACGTCCTG GACCGGATGC CCCGCGACAG CCTGGAAAAC CTGGTGGGGA CGACGGAAGC 53640

GGCGGCGCCG TGAAGCGGCA GCCGGACTTC GCGGCCCACG GCCGGGCGGT CGACCGGGTG 53700

CTGGCCGGCC GGCTGAGCGC GGCGCTGGCC CGGCCGGCCG CGCAGCAGCC GGGCTGGCCG 53760

GACGCCGAGC GGGCGGCCGA GGTGAATTC 53789

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 4572 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Met Phe Tyr Thr Ser Gly Thr Thr Gly Arg Pro Lys Gly Val Val Ser
1 5 10 15

Thr Gln Arg Asn Cys Leu Trp Ser Val Ala Ser Cys Tyr Val Pro Phe
20 25 30

Pro Gly Leu Ser Asp Gln Asp Arg Val Leu Trp Pro Leu Pro Leu Phe
35 40 45

His Ser Leu Ser His Ile Ala Cys Val Leu Ser Ala Thr Val Val Gly
50 55 60

Ala Ser Val Arg Ile Ala Asp Gly Ser Ser Ala Asp Asp Val Met Arg
65 70 75 80

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Leu Ile Glu Ala Glu Ser Ser Thr Phe Leu Ala Gly Val Pro Thr Thr
                85                  90                  95

Tyr His His Leu Val Arg Ala Ala Arg Gln Arg Gly Phe Ser Ala Pro
            100                 105                 110

Ser Leu Arg Ile Gly Leu Ala Gly Gly Ala Val Leu Gly Ala Gly Leu
        115                 120                 125

Arg Ser Glu Phe Glu Glu Thr Phe Gly Val Pro Leu Ile Asp Ala Tyr
    130                 135                 140

Gly Ser Thr Glu Thr Cys Gly Ala Ile Thr Met Asn Pro Pro Asp Gly
145                 150                 155                 160

Ala Arg Val Glu Gly Ser Cys Gly Leu Ala Val Pro Gly Val Asp Val
                165                 170                 175

Arg Val Val Asp Pro Asp Thr Gly Leu Asp Val Pro Ala Gly Glu Glu
            180                 185                 190

Gly Glu Val Trp Val Ser Gly Pro Asn Val Met Leu Gly Tyr His Asn
        195                 200                 205

Ser Pro Glu Ala Thr Ala Ala Ala Met Arg Asp Gly Trp Phe Arg Thr
    210                 215                 220

Gly Asp Leu Ala Arg Arg Asp Asp Ala Gly Tyr Phe Thr Ile Cys Gly
225                 230                 235                 240

Arg Ile Lys Glu Leu Ile Ile Arg Gly Gly Ala Asn Ile His Pro Gly
                245                 250                 255

Glu Val Glu Ala Val Leu Arg Thr Val Asp Gly Val Ala Asp Ala Ala
            260                 265                 270
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Val Gly Gly Val Pro His Asp Thr Leu Gly Glu Val Pro Val Ala Tyr
275 280 285

Val Ile Pro Gly Pro Thr Gly Phe Asp Pro Ala Ala Leu Ile Glu Lys
290 295 300

Cys Arg Glu Gln Leu Ser Ala Tyr Lys Val Pro Asp Arg Ile Leu Glu
305 310 315 320

Val Ala His Ile Pro Arg Thr Ala Ser Gly Lys Ile Arg Arg Gly Leu
325 330 335

Leu Thr Asp Glu Pro Ala Gln Leu Arg Tyr Ala Ala Thr Glu His Glu
340 345 350

Glu Gln Ser Arg His Ala Asp Glu Ser Val Ala Ala Ala Leu Arg Ala
355 360 365

Arg Leu Ser Gly Leu Asp Glu Arg Ala Gln Cys Glu Leu Leu Glu Asp
370 375 380

Leu Val Arg Thr Gln Ala Ala Asp Val Leu Gly Gln Pro Val Pro Asp
385 390 395 400

Gly Arg Ala Phe Arg Asp Leu Gly Phe Thr Ser Leu Ala Ile Val Glu
405 410 415

Leu Arg Asn Arg Leu Thr Glu His Thr Gly Leu Trp Leu Pro Ala Ser
420 425 430

Ala Val Phe Asp His Pro Thr Pro Ala Ala Leu Ala Ala Arg Val Arg
435 440 445

Ala Glu Leu Leu Gly Ile Thr Gln Ala Val Ala Glu Pro Val Val Ala
450 455 460

Ala Asp Pro Gly Glu Pro Ile Ala Ile Val Gly Met Ala Cys Arg Leu

465 470 475 480

Pro Gly Gly Val Ala Ser Pro Glu Asp Leu Trp Arg Leu Val Ala Glu
485 490 495

Arg Val Asp Ala Val Ser Glu Phe Pro Gly Asp Arg Gly Trp Asp Leu
500 505 510

Asp Ser Leu Ile Asp Pro Asp Arg Glu Arg Ala Gly Thr Ser Tyr Val
515 520 525

Gly Gln Gly Gly Phe Leu His Asp Ala Gly Glu Phe Asp Ala Gly Phe
530 535 540

Phe Gly Ile Ser Pro Arg Glu Ala Val Ala Met Asp Pro Gln Gln Arg
545 550 555 560

Leu Leu Leu Glu Thr Ser Trp Glu Ala Leu Glu Asn Ala Gly Val Asp
565 570 575

Pro Ile Ala Leu Lys Gly Thr Asp Thr Gly Val Phe Ser Gly Leu Met
580 585 590

Gly Gln Gly Tyr Gly Ser Gly Ala Val Ala Pro Glu Leu Glu Gly Phe
595 600 605

Val Thr Thr Gly Val Ala Ser Ser Val Ala Ser Gly Arg Val Ser Tyr
610 615 620

Val Leu Gly Leu Glu Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser
625 630 635 640

Ser Ser Leu Val Ala Met His Leu Ala Ala Gln Ala Leu Arg Gln Gly
645 650 655

Glu Cys Ser Met Ala Leu Ala Gly Gly Val Thr Val Met Ala Thr Pro
660 665 670

Gly Ser Phe Val Glu Phe Ser Arg Gln Arg Ala Leu Ala Pro Asp Gly
675 680 685

Arg Cys Lys Ala Phe Ala Ala Ala Ala Asp Gly Thr Gly Trp Ser Glu
690 695 700

Gly Val Gly Val Val Val Leu Glu Arg Leu Ser Val Ala Arg Glu Arg
705 710 715 720

Gly His Arg Ile Leu Ala Val Leu Arg Gly Ser Ala Val Asn Gln Asp
725 730 735

Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Leu Ser Gln Gln Arg
740 745 750

Val Ile Arg Arg Ala Leu Ala Ala Ala Gly Leu Ala Pro Ser Asp Val
755 760 765

Asp Val Val Glu Ala His Gly Thr Gly Thr Thr Leu Gly Asp Pro Ile
770 775 780

Glu Ala Gln Ala Leu Leu Ala Thr Tyr Gly Gln Glu Arg Lys Gln Pro
785 790 795 800

Leu Trp Leu Gly Ser Leu Lys Ser Asn Ile Gly His Ala Gln Ala Ala
805 810 815

Ala Gly Val Ala Gly Val Ile Lys Met Val Gln Ala Leu Arg His Glu
820 825 830

Thr Leu Pro Pro Thr Leu His Val Asp Lys Pro Thr Leu Glu Val Asp
835 840 845

Trp Ser Ala Gly Ala Ile Glu Leu Leu Thr Glu Ala Arg Ala Trp Pro
850 855 860

Arg Asn Gly Arg Pro Arg Arg Ala Gly Val Ser Ser Phe Gly Val Ser
865 870 875 880

Gly Thr Asn Ala His Leu Ile Leu Glu Glu Ala Pro Ala Glu Glu Pro
885 890 895

Val Ala Ala Pro Glu Leu Pro Val Val Pro Leu Val Val Ser Ala Arg
900 905 910

Ser Thr Glu Ser Leu Ser Gly Gln Ala Glu Arg Leu Ala Ser Leu Leu
915 920 925

Glu Gly Asp Val Ser Leu Thr Glu Val Ala Gly Ala Leu Val Ser Arg
930 935 940

Arg Ala Val Leu Asp Glu Arg Ala Val Val Val Ala Gly Ser Arg Glu
945 950 955 960

Glu Ala Val Thr Gly Leu Arg Ala Leu Asn Thr Ala Gly Ser Gly Thr
965 970 975

Pro Gly Lys Val Val Trp Val Phe Pro Gly Gln Gly Thr Gln Trp Ala
980 985 990

Gly Met Gly Arg Glu Leu Leu Ala Glu Ser Pro Val Phe Ala Glu Arg
995 1000 1005

Ile Ala Glu Cys Ala Ala Ala Leu Ala Pro Trp Ile Asp Trp Ser Leu
1010 1015 1020

Val Asp Val Leu Arg Gly Glu Gly Asp Leu Gly Arg Val Asp Val Leu
1025 1030 1035 1040

Gln Pro Ala Cys Phe Ala Val Met Val Gly Leu Ala Ala Val Trp Glu
1045 1050 1055

Ser Val Gly Val Arg Pro Asp Ala Val Val Gly His Ser Gln Gly Glu

1060 1065 1070

Ile Ala Ala Ala Cys Val Ser Gly Ala Leu Ser Leu Glu Asp Ala Ala
1075 1080 1085

Lys Val Val Ala Leu Arg Ser Gln Ala Ile Ala Ala Glu Leu Ser Gly
1090 1095 1100

Arg Gly Gly Met Ala Ser Val Ala Leu Gly Glu Asp Asp Val Val Ser
1105 1110 1115 1120

Arg Leu Val Asp Gly Val Glu Val Ala Ala Val Asn Gly Pro Ser Ser
1125 1130 1135

Val Val Ile Ala Gly Asp Ala His Ala Leu Asp Ala Thr Leu Glu Ile
1140 1145 1150

Leu Ser Gly Glu Gly Ile Arg Val Arg Arg Val Ala Val Asp Tyr Ala
1155 1160 1165

Ser His Thr Arg His Val Glu Asp Ile Arg Asp Thr Leu Ala Glu Thr
1170 1175 1180

Leu Ala Gly Ile Ser Ala Gln Ala Pro Ala Val Pro Phe Tyr Ser Thr
1185 1190 1195 1200

Val Thr Ser Glu Trp Val Arg Asp Ala Gly Val Leu Asp Gly Gly Tyr
1205 1210 1215

Trp Tyr Arg Asn Leu Arg Asn Gln Val Arg Phe Gly Ala Ala Ala Thr
1220 1225 1230

Ala Leu Leu Glu Gln Gly His Thr Val Phe Val Glu Val Ser Ala His
1235 1240 1245

Pro Val Thr Val Gln Pro Leu Ser Glu Leu Thr Gly Asp Ala Ile Gly
1250 1255 1260

Thr Leu Arg Arg Glu Asp Gly Gly Leu Arg Arg Leu Leu Ala Ser Met
1265 1270 1275 1280

Gly Glu Leu Phe Val Arg Gly Ile Asp Val Asp Trp Thr Ala Met Val
1285 1290 1295

Pro Ala Ala Gly Trp Val Asp Leu Pro Thr Tyr Ala Phe Glu His Arg
1300 1305 1310

His Tyr Trp Leu Glu Pro Ala Glu Pro Ala Ser Ala Gly Asp Pro Leu
1315 1320 1325

Leu Gly Thr Val Val Ser Thr Pro Gly Ser Asp Arg Leu Thr Ala Val
1330 1335 1340

Ala Gln Trp Ser Arg Arg Ala Gln Pro Trp Ala Val Asp Gly Leu Val
1345 1350 1355 1360

Pro Asn Ala Ala Leu Val Glu Ala Ala Ile Arg Leu Gly Asp Leu Ala
1365 1370 1375

Gly Thr Pro Val Val Gly Glu Leu Val Val Asp Ala Pro Val Val Leu
1380 1385 1390

Pro Arg Arg Gly Ser Arg Glu Val Gln Leu Ile Val Gly Glu Pro Gly
1395 1400 1405

Glu Gln Arg Arg Arg Pro Ile Glu Val Phe Ser Arg Glu Ala Asp Glu
1410 1415 1420

Pro Trp Thr Arg His Ala His Gly Thr Leu Ala Pro Ala Ala Ala Ala
1425 1430 1435 1440

Val Pro Glu Pro Ala Ala Ala Gly Asp Ala Thr Asp Val Thr Val Ala
1445 1450 1455

Gly Leu Arg Asp Ala Asp Arg Tyr Gly Ile His Pro Ala Leu Leu Asp
1460 1465 1470

Ala Ala Val Arg Thr Val Val Gly Asp Asp Leu Leu Pro Ser Val Trp
1475 1480 1485

Thr Gly Val Ser Leu Leu Ala Ser Gly Ala Thr Ala Val Thr Val Thr
1490 1495 1500

Pro Thr Ala Thr Gly Leu Arg Leu Thr Asp Pro Ala Gly Gln Pro Val
1505 1510 1515 1520

Leu Thr Val Glu Ser Val Arg Gly Thr Pro Phe Val Ala Glu Gln Gly
1525 1530 1535

Thr Thr Asp Ala Leu Phe Arg Val Asp Trp Pro Glu Ile Pro Leu Pro
1540 1545 1550

Thr Ala Glu Thr Ala Asp Phe Leu Pro Tyr Glu Ala Thr Ser Ala Glu
1555 1560 1565

Ala Thr Leu Ser Ala Leu Gln Ala Trp Leu Ala Asp Pro Ala Glu Thr
1570 1575 1580

Arg Leu Ala Val Val Thr Gly Asp Cys Thr Glu Pro Gly Ala Ala Ala
1585 1590 1595 1600

Ile Trp Gly Leu Val Arg Ser Ala Gln Ser Glu His Pro Gly Arg Ile
1605 1610 1615

Val Leu Ala Asp Leu Asp Asp Pro Ala Val Leu Pro Ala Val Val Ala
1620 1625 1630

Ser Gly Glu Pro Gln Val Arg Val Arg Asn Gly Val Ala Ser Val Pro
1635 1640 1645

Arg Leu Thr Arg Val Thr Pro Arg Gln Asp Ala Arg Pro Leu Asp Pro

1650 1655 1660

Glu Gly Thr Val Leu Ile Thr Gly Gly Thr Gly Thr Leu Gly Ala Leu
1665 1670 1675 1680

Thr Ala Arg His Leu Val Thr Ala His Gly Val Arg His Leu Val Leu
1685 1690 1695

Val Ser Arg Arg Gly Glu Ala Pro Glu Leu Gln Glu Glu Leu Thr Ala
1700 1705 1710

Leu Gly Ala Ser Val Ala Ile Ala Ala Cys Asp Val Ala Asp Arg Ala
1715 1720 1725

Gln Leu Glu Ala Val Leu Arg Ala Ile Pro Ala Glu His Pro Leu Thr
1730 1735 1740

Ala Val Ile His Thr Ala Gly Val Leu Asp Asp Gly Val Val Thr Glu
1745 1750 1755 1760

Leu Thr Pro Asp Arg Leu Ala Thr Val Arg Arg Pro Lys Val Asp Ala
1765 1770 1775

Ala Arg Leu Leu Asp Glu Leu Thr Arg Glu Ala Asp Leu Ala Ala Phe
1780 1785 1790

Val Leu Phe Ser Ser Ala Ala Gly Val Leu Gly Asn Pro Gly Gln Ala
1795 1800 1805

Gly Tyr Ala Ala Ala Asn Ala Glu Leu Asp Ala Leu Ala Arg Gln Arg
1810 1815 1820

Asn Ser Leu Asp Leu Pro Ala Val Ser Ile Ala Trp Gly Tyr Trp Ala
1825 1830 1835 1840

Thr Val Ser Gly Met Thr Glu His Leu Gly Asp Ala Asp Leu Arg Arg
1845 1850 1855

Asn Gln Arg Ile Gly Met Ser Gly Leu Pro Ala Asp Glu Gly Met Ala
1860 1865 1870

Leu Leu Asp Ala Ala Ile Ala Thr Gly Gly Thr Leu Val Ala Ala Lys
1875 1880 1885

Phe Asp Val Ala Ala Leu Arg Ala Thr Ala Lys Ala Gly Gly Pro Val
1890 1895 1900

Pro Pro Leu Leu Arg Gly Leu Ala Pro Leu Pro Arg Arg Ala Ala Ala
1905 1910 1915 1920

Lys Thr Ala Ser Leu Thr Glu Arg Leu Ala Gly Leu Ala Glu Thr Glu
1925 1930 1935

Gln Ala Ala Ala Leu Leu Asp Leu Val Arg Arg His Ala Ala Glu Val
1940 1945 1950

Leu Gly His Ser Gly Ala Glu Ser Val His Ser Gly Arg Thr Phe Lys
1955 1960 1965

Asp Ala Gly Phe Asp Ser Leu Thr Ala Val Glu Leu Arg Asn Arg Leu
1970 1975 1980

Ala Ala Ala Thr Gly Leu Thr Leu Ser Pro Ala Met Ile Phe Asp Tyr
1985 1990 1995 2000

Pro Lys Pro Pro Ala Leu Ala Asp His Leu Arg Ala Lys Leu Phe Gly
2005 2010 2015

Ser Ala Ala Asn Arg Pro Ala Glu Ile Gly Thr Ala Ala Ala Glu Glu
2020 2025 2030

Pro Ile Ala Ile Val Ala Met Ala Cys Arg Phe Pro Gly Gly Val His
2035 2040 2045

Ser Pro Glu Asp Leu Trp Arg Leu Val Ala Asp Gly Ala Asp Ala Val
2050 2055 2060

Thr Glu Phe Pro Ala Asp Arg Gly Trp Asp Thr Asp Arg Leu Tyr His
2065 2070 2075 2080

Glu Asp Pro Asp His Glu Gly Thr Thr Tyr Val Arg His Gly Ala Phe
2085 2090 2095

Leu Asp Asp Ala Ala Gly Phe Asp Ala Ala Phe Phe Gly Ile Ser Pro
2100 2105 2110

Asn Glu Ala Leu Ala Met Asp Pro Gln Gln Arg Leu Leu Leu Glu Thr
2115 2120 2125

Ser Trp Glu Leu Phe Glu Arg Ala Ala Ile Asp Pro Thr Thr Leu Ala
2130 2135 2140

Gly Gln Asp Ile Gly Val Phe Ala Gly Val Asn Ser His Asp Tyr Ser
2145 2150 2155 2160

Met Arg Met His Arg Ala Ala Gly Val Glu Gly Phe Arg Leu Thr Gly
2165 2170 2175

Gly Ser Ala Ser Val Leu Ser Gly Arg Val Ala Tyr His Phe Gly Val
2180 2185 2190

Glu Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser Ser Leu Val
2195 2200 2205

Ala Leu His Met Ala Val Gln Ala Leu Gln Arg Gly Glu Cys Ser Met
2210 2215 2220

Ala Leu Ala Gly Gly Val Met Val Met Gly Thr Val Glu Thr Phe Val
2225 2230 2235 2240

Glu Phe Ser Arg Gln Arg Gly Leu Ala Pro Asp Gly Arg Cys Lys Ala

2245 2250 2255

Phe Ala Asp Gly Ala Asp Gly Thr Gly Trp Ser Glu Gly Val Gly Leu
2260 2265 2270

Leu Leu Val Glu Arg Leu Ser Glu Ala Gln Arg Arg Gly His Gln Val
2275 2280 2285

Leu Ala Val Val Arg Gly Ser Ala Val Asn Ser Asp Gly Ala Ser Asn
2290 2295 2300

Gly Leu Thr Ala Pro Asn Gly Pro Ser Gln Gln Arg Val Ile Arg Lys
2305 2310 2315 2320

Ala Leu Ala Ala Ala Gly Leu Ser Thr Ser Asp Val Asp Ala Val Glu
2325 2330 2335

Ala His Gly Thr Gly Thr Thr Leu Gly Asp Pro Ile Glu Ala Glu Ala
2340 2345 2350

Leu Leu Ala Thr Tyr Gly Gln Asn Arg Glu Thr Pro Leu Trp Leu Gly
2355 2360 2365

Ser Val Lys Ser Asn Leu Gly His Thr Gln Ala Ala Ala Gly Val Ala
2370 2375 2380

Gly Val Ile Lys Met Val Met Ala Met Arg His Gly Val Leu Pro Arg
2385 2390 2395 2400

Thr Leu His Val Asp Arg Pro Ser Ser Tyr Val Asp Trp Ser Ala Gly
2405 2410 2415

Ala Val Glu Leu Leu Thr Glu Ala Arg Asp Trp Val Ser Asn Gly His
2420 2425 2430

Pro Arg Arg Ala Gly Val Ser Ser Phe Gly Ile Gly Gly Thr Asn Ala
2435 2440 2445

His Val Val Leu Glu Glu Val Ala Ala Pro Ile Thr Thr Pro Gln Pro
2450 2455 2460

Glu Pro Ala Glu Phe Leu Val Pro Val Leu Val Ser Ala Arg Thr Ala
2465 2470 2475 2480

Ala Gly Leu Arg Gly Gln Ala Gly Arg Leu Ala Ala Phe Leu Gly Asp
2485 2490 2495

Arg Thr Asp Val Arg Val Pro Asp Ala Ala Tyr Ala Leu Ala Thr Thr
2500 2505 2510

Arg Ala Gln Leu Asp His Arg Ala Val Val Leu Ala Ser Asp Arg Ala
2515 2520 2525

Gln Leu Cys Ala Asp Leu Ala Ala Phe Gly Ser Gly Val Val Thr Gly
2530 2535 2540

Thr Pro Val Asp Gly Lys Leu Ala Val Leu Phe Thr Gly Gln Gly Ser
2545 2550 2555 2560

Gln Trp Ala Gly Met Gly Arg Glu Leu Ala Glu Thr Phe Pro Val Phe
2565 2570 2575

Arg Asp Ala Phe Glu Ala Ala Cys Glu Ala Val Asp Thr His Leu Arg
2580 2585 2590

Glu Arg Pro Leu Arg Glu Val Val Phe Asp Asp Ser Ala Leu Leu Asp
2595 2600 2605

Gln Thr Met Tyr Thr Gln Gly Ala Leu Phe Ala Val Glu Thr Ala Leu
2610 2615 2620

Phe Arg Leu Phe Glu Ser Trp Gly Val Arg Pro Gly Leu Leu Ala Gly
2625 2630 2635 2640

His Ser Ile Gly Glu Leu Ala Ala Ala His Val Ser Gly Val Leu Asp
2645 2650 2655

Leu Ala Asp Ala Gly Glu Leu Val Ala Ala Arg Gly Arg Leu Met Gln
2660 2665 2670

Ala Leu Pro Ala Gly Gly Ala Met Val Ala Val Gln Ala Thr Glu Asp
2675 2680 2685

Glu Val Ala Pro Leu Leu Asp Gly Thr Val Cys Val Ala Ala Val Asn
2690 2695 2700

Gly Pro Asp Ser Val Val Leu Ser Gly Thr Glu Ala Ala Val Leu Ala
2705 2710 2715 2720

Val Ala Asp Glu Leu Ala Gly Arg Gly Arg Lys Thr Arg Arg Leu Ala
2725 2730 2735

Val Ser His Ala Phe His Ser Pro Leu Met Glu Pro Met Leu Asp Asp
2740 2745 2750

Phe Arg Ala Val Ala Glu Arg Leu Thr Tyr Arg Ala Gly Ser Leu Pro
2755 2760 2765

Val Val Ser Thr Leu Thr Gly Glu Leu Ala Ala Leu Asp Ser Pro Asp
2770 2775 2780

Tyr Trp Val Gly Gln Val Arg Asn Ala Val Arg Phe Ser Asp Ala Val
2785 2790 2795 2800

Thr Ala Leu Gly Ala Gln Gly Ala Ser Thr Phe Leu Glu Leu Gly Pro
2805 2810 2815

Gly Gly Ala Leu Ala Ala Met Ala Leu Gly Thr Leu Gly Gly Pro Glu
2820 2825 2830

Gln Ser Cys Val Ala Thr Leu Arg Lys Asn Gly Ala Glu Val Pro Asp

2835 2840 2845

Val Leu Thr Ala Leu Ala Glu Leu His Val Arg Gly Val Gly Val Asp
2850 2855 2860

Trp Thr Thr Val Leu Asp Glu Pro Ala Thr Ala Val Gly Thr Val Leu
2865 2870 2875 2880

Pro Thr Tyr Ala Phe Gln His Gln Arg Phe Trp Val Asp Val Asp Glu
2885 2890 2895

Thr Ala Ala Val Ser Val Thr Pro Pro Pro Ala Glu Pro Ile Val Asp
2900 2905 2910

Arg Pro Val Gln Asp Val Leu Glu Leu Val Arg Glu Ser Ala Ala Val
2915 2920 2925

Val Leu Gly His Arg Asp Ala Gly Ser Phe Asp Leu Asp Arg Ser Phe
2930 2935 2940

Lys Asp His Gly Phe Asp Ser Leu Ser Ala Val Lys Leu Arg Asn Arg
2945 2950 2955 2960

Leu Arg Asp Phe Thr Gly Val Glu Leu Pro Ser Thr Leu Ile Phe Asp
2965 2970 2975

Tyr Pro Asn Pro Ala Val Leu Ala Asp His Leu Arg Ala Glu Leu Leu
2980 2985 2990

Gly Glu Arg Pro Ala Ala Pro Ala Pro Val Thr Arg Asp Val Ser Asp
2995 3000 3005

Glu Pro Ile Ala Ile Val Gly Met Ser Thr Arg Leu Pro Gly Gly Ala
3010 3015 3020

Asp Ser Pro Glu Glu Leu Trp Lys Leu Val Ala Glu Gly Arg Asp Ala
3025 3030 3035 3040

Val Ser Gly Phe Pro Val Asp Arg Gly Trp Asp Leu Asp Gly Leu Tyr
3045 3050 3055

His Pro Asp Pro Ala His Ala Gly Thr Ser Tyr Thr Arg Ser Gly Gly
3060 3065 3070

Phe Leu His Asp Ala Ala Gln Phe Asp Ala Gly Leu Phe Gly Ile Ser
3075 3080 3085

Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg Leu Leu Leu Glu
3090 3095 3100

Thr Ser Trp Glu Ala Leu Glu Arg Ala Gly Val Asp Pro Leu Ser Ala
3105 3110 3115 3120

Arg Gly Ser Asp Val Gly Val Phe Thr Gly Ile Val His His Asp Tyr
3125 3130 3135

Val Thr Arg Leu Arg Glu Val Pro Glu Asp Val Gln Gly Tyr Thr Met
3140 3145 3150

Thr Gly Thr Ala Ser Ser Val Ala Ser Gly Arg Val Ala Tyr Val Phe
3155 3160 3165

Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser Ser
3170 3175 3180

Leu Val Ala Met His Leu Ala Ala Gln Ala Leu Arg Gln Gly Glu Cys
3185 3190 3195 3200

Ser Met Ala Leu Ala Gly Gly Ala Thr Val Met Ala Ser Pro Asp Ala
3205 3210 3215

Phe Leu Glu Phe Ser Arg Gln Arg Gly Leu Ser Ala Asp Gly Arg Cys
3220 3225 3230

Lys Ala Tyr Ala Glu Gly Ala Asp Gly Thr Gly Trp Ala Glu Gly Val
3235 3240 3245

Gly Val Val Val Leu Glu Arg Leu Ser Val Ala Arg Glu Arg Gly His
3250 3255 3260

Arg Val Leu Ala Val Leu Arg Gly Ser Ala Val Asn Gln Asp Gly Ala
3265 3270 3275 3280

Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser Gln Gln Arg Val Ile
3285 3290 3295

Arg Gly Ala Leu Ala Ser Ala Gly Leu Ala Pro Ser Asp Val Asp Val
3300 3305 3310

Val Glu Gly His Gly Thr Gly Thr Ala Leu Gly Asp Pro Ile Glu Val
3315 3320 3325

Gln Ala Leu Leu Ala Thr Tyr Gly Gln Glu Arg Glu Gln Pro Leu Trp
3330 3335 3340

Leu Gly Ser Leu Lys Ser Asn Leu Gly His Thr Gln Ala Ala Ala Gly
3345 3350 3355 3360

Val Val Gly Val Ile Lys Met Ile Met Ala Met Arg His Gly Val Met
3365 3370 3375

Pro Ala Thr Leu His Val Asp Glu Arg Thr Ser Gln Val Asp Trp Ser
3380 3385 3390

Ala Gly Ala Ile Glu Val Leu Thr Glu Ala Arg Glu Trp Pro Arg Thr
3395 3400 3405

Gly Arg Pro Arg Arg Ala Gly Val Ser Ser Phe Gly Ala Ser Gly Thr
3410 3415 3420

Asn Ala His Leu Ile Ile Glu Glu Gly Pro Ala Glu Glu Ala Val Asp

3425 3430 3435 3440

Glu Glu Val Ala Ser Val Val Pro Leu Val Val Ser Ala Arg Ser Ala
3445 3450 3455

Gly Ser Leu Ala Gly Gln Ala Gly Arg Leu Ala Ala Val Leu Glu Asn
3460 3465 3470

Glu Ser Leu Ala Gly Val Ala Gly Ala Leu Val Ser Gly Arg Ala Thr
3475 3480 3485

Leu Asn Glu Arg Ala Val Val Ile Ala Gly Ser Arg Asp Glu Ala Gln
3490 3495 3500

Asp Gly Leu Gln Ala Leu Ala Arg Gly Glu Asn Ala Pro Gly Val Val
3505 3510 3515 3520

Thr Gly Thr Ala Gly Lys Pro Gly Lys Val Val Trp Val Phe Pro Gly
3525 3530 3535

Gln Gly Ser Gln Trp Met Gly Met Gly Arg Asp Leu Leu Asp Ser Ser
3540 3545 3550

Pro Val Phe Ala Ala Arg Ile Lys Glu Cys Ala Ala Ala Leu Glu Gln
3555 3560 3565

Trp Thr Asp Trp Ser Leu Leu Asp Val Leu Arg Gly Asp Ala Asp Leu
3570 3575 3580

Leu Asp Arg Val Asp Val Val Gln Pro Ala Ser Phe Ala Met Met Val
3585 3590 3595 3600

Gly Leu Ala Ala Val Trp Thr Ser Leu Gly Val Thr Pro Asp Ala Val
3605 3610 3615

Leu Gly His Ser Gln Gly Glu Ile Ala Ala Ala Cys Val Ser Gly Ala
3620 3625 3630

Leu Ser Leu Asp Asp Ala Ala Lys Val Val Ala Leu Arg Ser Gln Ala
3635 3640 3645

Ile Ala Gly Glu Leu Ala Gly Arg Gly Gly Met Ala Ser Val Ala Leu
3650 3655 3660

Ser Glu Glu Asp Ala Val Ala Arg Leu Thr Pro Trp Ala Asn Arg Val
3665 3670 3675 3680

Glu Val Ala Ala Val Asn Ser Pro Ser Ser Val Val Ile Ala Gly Asp
3685 3690 3695

Ala Gln Ala Leu Asp Glu Ala Leu Glu Ala Leu Ala Gly Asp Gly Val
3700 3705 3710

Arg Val Arg Arg Val Ala Val Asp Tyr Ala Ser His Thr Arg His Val
3715 3720 3725

Glu Ala Ile Ala Glu Thr Leu Ala Lys Thr Leu Ala Gly Ile Asp Ala
3730 3735 3740

Arg Val Pro Ala Ile Pro Phe Tyr Ser Thr Val Leu Gly Thr Trp Ile
3745 3750 3755 3760

Glu Gln Ala Val Val Asp Ala Gly Tyr Trp Tyr Arg Asn Leu Arg Gln
3765 3770 3775

Gln Val Arg Phe Gly Pro Ser Val Ala Asp Leu Ala Gly Leu Gly His
3780 3785 3790

Thr Val Phe Val Glu Ile Ser Ala His Pro Val Leu Val Gln Pro Leu
3795 3800 3805

Ser Glu Ile Ser Asp Asp Ala Val Val Thr Gly Ser Leu Arg Arg Asp
3810 3815 3820

Asp Gly Gly Leu Arg Arg Leu Leu Ala Ser Ala Ala Glu Leu Tyr Val
3825 3830 3835 3840

Arg Gly Val Ala Val Asp Trp Thr Ala Ala Val Pro Ala Ala Gly Trp
3845 3850 3855

Val Asp Leu Pro Thr Tyr Ala Phe Asp Arg Arg His Phe Trp Leu His
3860 3865 3870

Glu Ala Glu Thr Ala Glu Ala Ala Glu Gly Met Asp Gly Glu Phe Trp
3875 3880 3885

Thr Ala Ile Glu Gln Ser Asp Val Asp Ser Leu Ala Glu Leu Leu Glu
3890 3895 3900

Leu Val Pro Glu Gln Arg Gly Ala Leu Ser Thr Val Val Pro Val Leu
3905 3910 3915 3920

Ala Gln Trp Arg Asp Arg Arg Arg Glu Arg Ser Thr Ala Glu Lys Leu
3925 3930 3935

Arg Tyr Gln Val Thr Trp Gln Pro Leu Glu Arg Glu Ala Ala Gly Val
3940 3945 3950

Pro Gly Gly Arg Trp Leu Ala Val Val Pro Ala Gly Thr Thr Asp Ala
3955 3960 3965

Leu Leu Lys Glu Leu Thr Gly Gln Gly Leu Asp Ile Val Arg Leu Glu
3970 3975 3980

Ile Glu Glu Ala Ser Arg Ala Gln Leu Ala Glu Gln Leu Arg Asn Val
3985 3990 3995 4000

Leu Ala Glu His Asp Leu Thr Gly Val Leu Ser Leu Leu Ala Leu Asp
4005 4010 4015

Gly Gly Pro Ala Asp Ala Ala Glu Ile Thr Ala Ser Thr Leu Ala Leu

4020 4025 4030

Val Gln Ala Leu Gly Asp Thr Thr Thr Ser Ala Pro Leu Trp Cys Leu
4035 4040 4045

Thr Ser Gly Ala Val Asn Ile Gly Ile Gln Asp Ala Val Thr Ala Pro
4050 4055 4060

Ala Gln Ala Ala Val Trp Gly Leu Gly Arg Ala Val Ala Leu Glu Arg
4065 4070 4075 4080

Leu Asp Arg Trp Gly Gly Leu Val Asp Leu Pro Ala Ala Ile Asp Ala
4085 4090 4095

Arg Thr Ala Gln Ala Leu Leu Gly Val Leu Asn Gly Ala Ala Gly Glu
4100 4105 4110

Asp Gln Leu Ala Val Arg Arg Ser Gly Val Tyr Arg Arg Arg Leu Val
4115 4120 4125

Arg Lys Pro Val Pro Glu Ser Ala Thr Ser Arg Trp Glu Pro Arg Gly
4130 4135 4140

Thr Val Leu Val Thr Gly Gly Ala Glu Gly Leu Gly Arg His Ala Ser
4145 4150 4155 4160

Val Trp Leu Ala Gln Ser Gly Ala Glu Arg Leu Ile Val Thr Gly Thr
4165 4170 4175

Asp Gly Val Asp Glu Leu Thr Ala Glu Leu Ala Glu Phe Gly Thr Thr
4180 4185 4190

Val Glu Phe Cys Ala Asp Thr Asp Arg Asp Ala Ile Ala Gln Leu Val
4195 4200 4205

Ala Asp Ser Glu Val Thr Ala Val Val His Ala Ala Asp Ile Ala Gln
4210 4215 4220

Thr Ser Ser Val Asp Asp Thr Gly Val Ala Asp Leu Asp Glu Val Phe
4225 4230 4235 4240

Ala Ala Lys Val Thr Thr Ala Val Trp Leu Asp Gln Leu Phe Glu Asp
4245 4250 4255

Thr Pro Leu Asp Ala Phe Val Val Phe Ser Ser Ile Ala Gly Ile Trp
4260 4265 4270

Gly Gly Gly Gly Gln Gly Pro Ala Gly Ala Ala Asn Ala Val Leu Asp
4275 4280 4285

Ala Leu Val Glu Trp Arg Arg Ala Arg Gly Leu Lys Ala Thr Ser Ile
4290 4295 4300

Ala Trp Gly Ala Leu Asp Gln Ile Gly Ile Gly Met Asp Glu Ala Ala
4305 4310 4315 4320

Leu Ala Gln Leu Arg Arg Arg Gly Val Ile Pro Met Ala Pro Pro Leu
4325 4330 4335

Ala Val Thr Ala Met Val Gln Ala Val Ala Gly Asn Glu Lys Ala Val
4340 4345 4350

Ala Val Ala Asp Met Asp Trp Ala Ala Phe Ile Pro Ala Phe Thr Ser
4355 4360 4365

Val Arg Pro Ser Pro Leu Phe Ala Asp Leu Pro Glu Ala Lys Ala Ile
4370 4375 4380

Leu Arg Ala Ala Gln Asp Asp Gly Glu Asp Gly Asp Thr Ala Ser Ser
4385 4390 4395 4400

Leu Ala Asp Ser Leu Arg Ala Val Pro Asp Ala Glu Gln Asn Arg Ile
4405 4410 4415

Leu Leu Lys Leu Val Arg Gly His Ala Ser Thr Val Leu Gly His Ser
4420 4425 4430

Gly Ala Glu Gly Ile Gly Pro Arg Gln Ala Phe Gln Glu Val Gly Phe
4435 4440 4445

Asp Ser Leu Ala Ala Val Asn Leu Arg Asn Ser Leu His Ala Ala Thr
4450 4455 4460

Gly Leu Arg Leu Pro Ala Thr Leu Ile Phe Asp Tyr Pro Thr Pro Glu
4465 4470 4475 4480

Ala Leu Val Gly Tyr Leu Arg Val Glu Leu Leu Arg Glu Ala Asp Asp
4485 4490 4495

Gly Leu Asp Gly Arg Glu Asp Asp Leu Arg Arg Val Leu Ala Ala Val
4500 4505 4510

Pro Phe Ala Arg Phe Lys Glu Ala Gly Val Leu Asp Thr Leu Leu Gly
4515 4520 4525

Leu Ala Asp Thr Gly Thr Glu Pro Gly Thr Asp Ala Glu Thr Thr Glu
4530 4535 4540

Ala Ala Pro Ala Ala Asp Asp Ala Glu Leu Ile Asp Ala Leu Asp Ile
4545 4550 4555 4560

Ser Gly Leu Val Gln Arg Ala Leu Gly Gln Thr Ser
4565 4570

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5069 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Met Ala Asn Gln Ser Trp Arg Lys Asn Met Ser Ala Pro Asn Glu Gln
1   5   10   15

Ile Val Asp Ala Leu Arg Ala Ser Leu Lys Glu Asn Val Arg Leu Gln
            20   25   30

Gln Glu Asn Ser Ala Leu Ala Ala Ala Ala Ala Glu Pro Val Ala Ile
        35   40   45

Val Ser Met Ala Cys Arg Tyr Ala Gly Gly Ile Arg Gly Pro Glu Asp
    50   55   60

Phe Trp Arg Val Val Ser Glu Gly Ala Asp Val Tyr Thr Gly Phe Pro
65   70   75   80

Glu Asp Arg Gly Trp Asp Val Glu Gly Leu Tyr His Pro Asp Pro Asp
                85   90   95

Asn Pro Gly Thr Thr Tyr Val Arg Glu Gly Ala Phe Leu Gln Asp Ala
            100   105   110

Ala Gln Phe Asp Ala Gly Phe Phe Gly Ile Ser Pro Arg Glu Ala Leu
        115   120   125

Ala Met Asp Pro Gln Gln Arg Gln Leu Leu Glu Val Ser Trp Glu Thr
    130   135   140

Leu Glu Arg Ala Gly Ile Asp Pro His Ser Val Arg Gly Ser Asp Ile
145   150   155   160

Gly Val Tyr Ala Gly Val Val His Gln Asp Tyr Ala Pro Asp Leu Ser
165 170 175

Gly Phe Glu Gly Phe Met Ser Leu Glu Arg Ala Leu Gly Thr Ala Gly
180 185 190

Gly Val Ala Ser Gly Arg Val Ala Tyr Thr Leu Gly Leu Glu Gly Pro
195 200 205

Ala Val Thr Val Asp Thr Met Cys Ser Ser Ser Leu Val Ala Ile His
210 215 220

Leu Ala Ala Gln Ala Leu Arg Arg Gly Glu Cys Ser Met Ala Leu Ala
225 230 235 240

Gly Gly Ser Thr Val Met Ala Thr Pro Gly Gly Phe Val Gly Phe Ala
245 250 255

Arg Gln Arg Ala Leu Ala Phe Asp Gly Arg Cys Lys Ser Tyr Ala Ala
260 265 270

Ala Ala Asp Gly Ser Gly Trp Ala Glu Gly Val Gly Val Leu Leu Leu
275 280 285

Glu Arg Leu Ser Val Ala Arg Glu Arg Gly His Gln Val Leu Ala Val
290 295 300

Ile Arg Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr
305 310 315 320

Ala Pro Asn Gly Pro Ala Gln Gln Arg Val Ile Arg Lys Ala Leu Ala
325 330 335

Ser Ala Gly Leu Thr Pro Ser Asp Val Asp Thr Val Glu Gly His Gly
340 345 350

Thr Gly Thr Val Leu Gly Asp Pro Ile Glu Val Gln Ala Leu Leu Ala
355 360 365

Thr Tyr Gly Gln Gly Arg Asp Pro Gln Gln Pro Leu Trp Leu Gly Ser
370 375 380

Val Lys Ser Val Val Gly His Thr Gln Ala Ala Ser Gly Val Ala Gly
385 390 395 400

Val Ile Lys Met Val Gln Ser Leu Arg His Gly Gln Leu Pro Ala Thr
405 410 415

Gln His Val Asp Ala Pro Thr Pro Gln Val Asp Trp Ser Ala Gly Ala
420 425 430

Ile Glu Leu Leu Ala Glu Gly Arg Glu Trp Pro Arg Asn Gly His Pro
435 440 445

Arg Arg Gly Gly Ile Ser Ser Phe Gly Ala Ser Gly Thr Asn Ala His
450 455 460

Met Ile Leu Glu Glu Ala Pro Glu Asp Glu Pro Val Thr Glu Ala Pro
465 470 475 480

Ala Pro Thr Gly Val Val Pro Leu Val Val Ser Ala Ala Thr Ala Ala
485 490 495

Ser Leu Ala Ala Gln Ala Gly Arg Leu Ala Glu Val Gly Asp Val Ser
500 505 510

Leu Ala Asp Val Ala Gly Thr Leu Val Ser Gly Arg Ala Met Leu Ser
515 520 525

Glu Arg Ala Val Val Val Ala Gly Ser His Glu Glu Ala Val Thr Gly
530 535 540

Leu Arg Ala Leu Ala Arg Gly Glu Ser Ala Pro Gly Leu Leu Ser Gly

545 550 555 560

Arg Gly Ser Gly Val Pro Gly Lys Val Val Trp Val Phe Pro Gly Gln
565 570 575

Gly Thr Gln Trp Ala Gly Met Gly Arg Glu Leu Leu Asp Ser Ser Glu
580 585 590

Val Phe Ala Ala Arg Ile Ala Glu Cys Glu Thr Ala Leu Gly Arg Trp
595 600 605

Val Asp Trp Ser Leu Thr Asp Val Leu Arg Gly Glu Ala Asp Leu Leu
610 615 620

Asp Arg Val Asp Val Val Gln Pro Ala Ser Phe Ala Val Met Val Gly
625 630 635 640

Leu Ala Ala Val Trp Ala Ser Leu Gly Val Glu Pro Glu Ala Val Val
645 650 655

Gly His Ser Gln Gly Glu Ile Ala Ala Ala Cys Val Ser Gly Ala Leu
660 665 670

Ser Leu Glu Asp Ala Ala Lys Val Val Ala Leu Arg Ser Gln Ala Ile
675 680 685

Ala Ala Ser Leu Ala Gly Arg Gly Gly Met Ala Ser Val Ala Leu Ser
690 695 700

Glu Glu Asp Ala Thr Ala Arg Leu Glu Pro Trp Ala Gly Arg Val Glu
705 710 715 720

Val Ala Ala Val Asn Gly Pro Thr Ser Val Val Ile Ala Gly Asp Ala
725 730 735

Glu Ala Leu Asp Glu Ala Leu Asp Ala Leu Asp Asp Gln Gly Val Arg
740 745 750

Ile Arg Arg Val Ala Val Asp Tyr Ala Ser His Thr Arg His Val Glu
755 760 765

Ala Ala Arg Asp Ala Leu Ala Glu Met Leu Gly Gly Ile Arg Ala Gln
770 775 780

Ala Pro Glu Val Pro Phe Tyr Ser Thr Val Thr Gly Gly Trp Val Glu
785 790 795 800

Asp Ala Gly Val Leu Asp Gly Gly Tyr Trp Tyr Arg Asn Leu Arg Arg
805 810 815

Gln Val Arg Phe Gly Pro Ala Val Ala Glu Leu Ile Glu Gln Gly His
820 825 830

Arg Val Phe Val Glu Val Ser Ala His Pro Val Leu Val Gln Pro Ile
835 840 845

Asn Glu Leu Val Asp Asp Thr Glu Ala Val Val Thr Gly Thr Leu Arg
850 855 860

Arg Glu Asp Gly Gly Leu Arg Arg Leu Leu Ala Ser Ala Ala Glu Leu
865 870 875 880

Phe Val Arg Gly Val Thr Val Asp Trp Ser Gly Val Leu Pro Pro Ser
885 890 895

Arg Arg Val Glu Leu Pro Thr Tyr Ala Phe Asp His Gln His Tyr Trp
900 905 910

Leu Gln Met Gly Gly Ser Ala Thr Asp Ala Val Ser Leu Gly Leu Ala
915 920 925

Gly Ala Asp His Pro Leu Leu Gly Ala Val Val Pro Leu Pro Gln Ser
930 935 940

Asp Gly Leu Val Phe Thr Ser Arg Leu Ser Leu Lys Ser His Pro Trp
945 950 955 960

Leu Ala Gly His Ala Ile Gly Gly Val Val Leu Ile Pro Gly Thr Val
965 970 975

Tyr Val Asp Leu Ala Leu Arg Ala Gly Asp Glu Leu Gly Phe Gly Val
980 985 990

Leu Glu Glu Leu Val Ile Glu Ala Pro Leu Val Leu Gly Glu Arg Gly
995 1000 1005

Gly Val Arg Val Gln Val Ala Val Ser Gly Pro Asn Glu Thr Gly Ser
1010 1015 1020

Arg Ala Val Asp Val Phe Ser Met Arg Glu Asp Gly Asp Glu Trp Thr
1025 1030 1035 1040

Arg His Ala Thr Gly Leu Leu Gly Ala Ser Thr Ser Arg Glu Pro Ser
1045 1050 1055

Arg Phe Asp Phe Ala Ala Trp Pro Pro Ala Gly Ala Glu Pro Ile Asp
1060 1065 1070

Val Glu Asn Phe Tyr Thr Asp Leu Thr Glu Arg Gly Tyr Ala Tyr Ser
1075 1080 1085

Gly Ala Phe Gln Gly Met Arg Ala Val Trp Arg Arg Gly Asp Glu Val
1090 1095 1100

Phe Ala Glu Val Ala Leu Pro Asp Asp His Arg Glu Asp Ala Gly Lys
1105 1110 1115 1120

Phe Gly Leu His Pro Ala Leu Leu Asp Ala Ala Leu His Thr Asn Ala
1125 1130 1135

Phe Ala Asn Pro Asp Asp Asp Arg Ser Val Leu Pro Phe Ala Trp Asn

1140 1145 1150

Gly Leu Val Leu His Ala Val Gly Ala Ser Ala Leu Arg Val Arg Val
1155 1160 1165

Ala Pro Gly Gly Pro Asp Ala Leu Thr Phe Gln Ala Ala Asp Glu Thr
1170 1175 1180

Gly Gly Leu Val Val Thr Met Asp Ser Leu Val Ser Arg Glu Val Ser
1185 1190 1195 1200

Ala Ala Gln Leu Glu Thr Ala Ala Gly Glu Glu Arg Asp Ser Leu Phe
1205 1210 1215

Gln Val Asp Trp Ile Glu Val Pro Ala Thr Glu Thr Ala Ala Thr Glu
1220 1225 1230

His Ala Glu Val Leu Glu Ala Phe Gly Glu Ala Ala Pro Leu Glu Leu
1235 1240 1245

Thr Ser Arg Val Leu Glu Ala Val Gln Ser Trp Leu Ala Asp Ala Ala
1250 1255 1260

Asp Glu Ala Arg Leu Val Val Val Thr Arg Gly Ala Val Arg Glu Val
1265 1270 1275 1280

Thr Asp Pro Ala Gly Ala Ala Val Trp Gly Leu Val Arg Ala Ala Gln
1285 1290 1295

Ala Glu Asn Pro Gly Arg Ile Ile Leu Val Asp Thr Asp Gly Asp Val
1300 1305 1310

Pro Leu Gly Ala Val Leu Ala Ser Gly Glu Pro Gln Leu Ala Val Arg
1315 1320 1325

Gly Asn Ala Phe Ser Val Pro Arg Leu Ala Arg Ala Thr Gly Glu Val
1330 1335 1340

Pro Glu Ala Pro Ala Val Phe Ser Pro Glu Gly Thr Val Leu Leu Thr
1345 1350 1355 1360

Gly Gly Thr Gly Ser Leu Gly Gly Leu Val Ala Lys His Leu Val Ala
1365 1370 1375

Arg His Gly Val Arg Arg Leu Val Leu Ala Ser Arg Arg Gly Val Ala
1380 1385 1390

Ala Glu Asp Leu Val Thr Glu Leu Thr Glu Gln Gly Ala Thr Val Ser
1395 1400 1405

Val Val Ala Cys Asp Val Ser Asp Arg Asp Gln Val Ala Ala Leu Leu
1410 1415 1420

Ala Glu His Arg Pro Thr Gly Ile Val His Leu Ala Gly Leu Leu Asp
1425 1430 1435 1440

Asp Gly Val Ile Gly Ala Leu Asn Arg Glu Arg Leu Ala Gly Val Phe
1445 1450 1455

Ala Pro Lys Val Asp Ala Val Gln His Leu Asp Glu Leu Thr Arg Asp
1460 1465 1470

Leu Gly Leu Asp Ala Phe Val Val Phe Ser Ser Ala Ala Ala Leu Met
1475 1480 1485

Gly Ser Ala Gly Gln Gly Asn Tyr Ala Ala Ala Asn Ala Phe Leu Asp
1490 1495 1500

Gly Leu Met Ala Gly Arg Arg Ala Ala Gly Leu Pro Gly Val Ser Leu
1505 1510 1515 1520

Ala Trp Gly Leu Trp Glu Gln Ala Asp Gly Leu Thr Ala Asn Leu Ser
1525 1530 1535

Ala Thr Asp Gln Ala Arg Met Ser Arg Gly Gly Val Leu Pro Met Thr
1540 1545 1550

Pro Ala Glu Ala Leu Asp Ile Phe Asp Ile Gly Leu Ala Ala Glu Gln
1555 1560 1565

Ala Leu Leu Val Pro Ile Lys Leu Asp Leu Arg Thr Leu Arg Gly Gln
1570 1575 1580

Ala Thr Ala Gly Gly Glu Val Pro His Leu Leu Arg Gly Leu Val Arg
1585 1590 1595 1600

Ala Ser Arg Arg Val Thr Arg Thr Ala Ala Ala Ser Gly Gly Gly Gly
1605 1610 1615

Leu Val His Lys Leu Ala Gly Arg Pro Ala Glu Glu Gln Glu Ala Val
1620 1625 1630

Leu Leu Gly Ile Val Gln Ala Glu Ala Ala Ala Val Leu Gly Phe Asn
1635 1640 1645

Ala Pro Glu Leu Ala Gln Gly Thr Arg Gly Phe Ser Asp Leu Gly Phe
1650 1655 1660

Asp Ser Leu Thr Ala Val Glu Leu Arg Asn Arg Leu Ser Ala Ala Thr
1665 1670 1675 1680

Gly Val Lys Leu Pro Ala Thr Leu Val Phe Asp Tyr Pro Thr Pro Val
1685 1690 1695

Ala Leu Ala Arg His Leu Arg Glu Glu Leu Gly Glu Thr Val Ala Gly
1700 1705 1710

Ala Pro Ala Thr Pro Val Thr Thr Val Ala Asp Ala Gly Glu Pro Ile
1715 1720 1725

Ala Ile Val Gly Met Ala Cys Arg Leu Pro Gly Gly Val Met Ser Pro

1730 1735 1740

Asp Asp Leu Trp Arg Met Val Ala Glu Gly Arg Asp Gly Met Ser Pro
1745 1750 1755 1760

Phe Pro Gly Asp Arg Gly Trp Asp Leu Asp Gly Leu Phe Asp Ser Asp
1765 1770 1775

Pro Glu Arg Pro Gly Thr Ala Tyr Ile Arg Gln Gly Gly Phe Leu His
1780 1785 1790

Glu Ala Ala Leu Phe Asp Pro Gly Phe Phe Gly Ile Ser Pro Arg Glu
1795 1800 1805

Ala Leu Ala Met Asp Pro Gln Gln Arg Leu Leu Leu Glu Ala Ser Trp
1810 1815 1820

Glu Ala Leu Glu Arg Ala Gly Ile Asp Pro Thr Lys Ala Arg Gly Asp
1825 1830 1835 1840

Ala Val Gly Val Phe Ser Gly Val Ser Ile His Asp Tyr Leu Glu Ser
1845 1850 1855

Leu Ser Asn Met Pro Ala Glu Leu Glu Gly Phe Val Thr Thr Ala Thr
1860 1865 1870

Ala Gly Ser Val Ala Ser Gly Arg Val Ser Tyr Thr Phe Gly Phe Glu
1875 1880 1885

Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser Ser Leu Val Ala
1890 1895 1900

Ile His Leu Ala Ala Gln Ala Leu Arg Gln Gly Glu Cys Thr Met Ala
1905 1910 1915 1920

Leu Ala Gly Gly Val Ala Val Met Gly Ser Pro Ile Gly Val Ile Gly
1925 1930 1935

Met Ser Arg Gln Arg Gly Met Ala Glu Asp Gly Arg Val Lys Ala Phe
1940 1945 1950

Ala Asp Gly Ala Asp Gly Thr Val Leu Ser Glu Gly Val Gly Ile Val
1955 1960 1965

Val Leu Glu Arg Leu Ser Val Ala Arg Glu Arg Gly His Arg Val Leu
1970 1975 1980

Ala Val Leu Arg Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly
1985 1990 1995 2000

Leu Thr Ala Pro Asn Gly Pro Ser Gln Gln Arg Val Ile Arg Ser Ala
2005 2010 2015

Leu Ala Gly Ala Gly Leu Gln Pro Ser Glu Val Asp Val Val Glu Ala
2020 2025 2030

His Gly Thr Gly Thr Ala Leu Gly Glu Pro Ile Glu Ala Gln Ala Leu
2035 2040 2045

Leu Ala Thr Tyr Gly Lys Ser Arg Glu Thr Pro Leu Trp Leu Gly Ser
2050 2055 2060

Leu Lys Ser Asn Ile Gly His Thr Gln Ala Ala Ala Gly Val Ala Ala
2065 2070 2075 2080

Val Ile Lys Met Val Gln Ala Leu Arg Gln Asp Thr Leu Pro Pro Thr
2085 2090 2095

Leu His Val Gln Glu Pro Thr Lys Gln Val Asp Trp Ser Ala Gly Ala
2100 2105 2110

Val Glu Leu Leu Thr Glu Gly Arg Glu Trp Ala Arg Asn Gly His Pro
2115 2120 2125

Arg Arg Ala Gly Val Ser Ser Phe Gly Ile Ser Gly Thr Asn Ala His
2130 2135 2140

Leu Ile Leu Glu Glu Ala Pro Ala Asp Asp Thr Ala Glu Ala Asp Val
2145 2150 2155 2160

Pro Asp Ala Val Val Pro Val Val Ile Ser Ala Arg Ser Thr Gly Ser
2165 2170 2175

Leu Ala Gly Gln Ala Gly Arg Leu Ala Ala Phe Leu Asp Gly Asp Val
2180 2185 2190

Pro Leu Thr Arg Val Ala Gly Ala Leu Leu Ser Thr Arg Ala Thr Leu
2195 2200 2205

Thr Asp Arg Ala Val Val Val Ala Gly Ser Ala Glu Glu Ala Arg Ala
2210 2215 2220

Gly Leu Thr Ala Leu Ala Arg Gly Glu Ser Ala Ser Gly Leu Val Thr
2225 2230 2235 2240

Gly Thr Ala Gly Met Pro Gly Lys Thr Val Trp Val Phe Pro Gly Gln
2245 2250 2255

Gly Thr Gln Trp Ala Gly Met Gly Arg Glu Leu Leu Glu Ala Ser Pro
2260 2265 2270

Val Phe Ala Glu Arg Ile Glu Glu Cys Ala Ala Ala Leu Gln Pro Trp
2275 2280 2285

Ile Asp Trp Ser Leu Leu Asp Val Leu Arg Gly Glu Gly Glu Leu Asp
2290 2295 2300

Arg Val Asp Val Leu Gln Pro Ala Cys Phe Ala Val Met Val Gly Leu
2305 2310 2315 2320

Ala Ala Val Trp Ala Ser Val Gly Val Val Pro Asp Ala Val Leu Gly

2325 2330 2335

His Ser Gln Gly Glu Ile Ala Ala Ala Cys Val Ser Gly Ala Leu Ser
2340 2345 2350

Leu Glu Asp Ala Ala Lys Val Val Ala Leu Arg Ser Gln Ala Ile Ala
2355 2360 2365

Ala Glu Leu Ser Gly Arg Gly Gly Met Ala Ser Ile Gln Leu Ser His
2370 2375 2380

Asp Glu Val Ala Ala Arg Leu Ala Pro Trp Ala Gly Arg Val Glu Ile
2385 2390 2395 2400

Ala Ala Val Asn Gly Pro Ala Ser Val Val Ile Ala Gly Asp Ala Glu
2405 2410 2415

Ala Leu Thr Glu Ala Val Glu Val Leu Gly Gly Arg Arg Val Ala Val
2420 2425 2430

Asp Tyr Ala Ser His Thr Arg His Val Glu Asp Ile Gln Asp Thr Leu
2435 2440 2445

Ala Glu Thr Leu Ala Gly Ile Asp Ala Gln Ala Pro Val Val Pro Phe
2450 2455 2460

Tyr Ser Thr Val Ala Gly Glu Trp Ile Thr Asp Ala Gly Val Val Asp
2465 2470 2475 2480

Gly Gly Tyr Trp Tyr Arg Asn Leu Arg Asn Gln Val Gly Phe Gly Pro
2485 2490 2495

Ala Val Ala Glu Leu Ile Glu Gln Gly His Gly Val Phe Val Glu Val
2500 2505 2510

Ser Ala His Pro Val Leu Val Gln Pro Ile Ser Glu Leu Thr Asp Ala
2515 2520 2525

Val Val Thr Gly Thr Leu Arg Arg Asp Asp Gly Gly Val Arg Arg Leu
2530 2535 2540

Leu Thr Ser Met Ala Glu Leu Phe Val Arg Gly Val Pro Val Asp Trp
2545 2550 2555 2560

Ala Thr Met Ala Pro Pro Ala Arg Val Glu Leu Pro Thr Tyr Ala Phe
2565 2570 2575

Asp His Gln His Phe Trp Leu Ser Pro Pro Ala Val Ala Asp Ala Pro
2580 2585 2590

Ala Leu Gly Leu Ala Gly Ala Asp His Pro Leu Leu Gly Ala Val Leu
2595 2600 2605

Pro Leu Pro Gln Ser Asp Gly Leu Val Phe Thr Ser Arg Leu Ser Val
2610 2615 2620

Arg Thr His Pro Trp Leu Ala Asp Gly Val Pro Ala Ala Ala Leu Val
2625 2630 2635 2640

Glu Leu Ala Val Arg Ala Gly Asp Glu Ala Gly Cys Pro Val Leu Ala
2645 2650 2655

Asp Leu Thr Val Glu Lys Leu Leu Val Leu Pro Glu Ser Gly Gly Leu
2660 2665 2670

Arg Val Gln Val Ile Val Ser Gly Glu Arg Thr Val Glu Val Tyr Ser
2675 2680 2685

Gln Leu Glu Gly Ala Glu Asp Trp Ile Arg Asn Ala Thr Gly His Leu
2690 2695 2700

Ser Ala Thr Ala Pro Ala His Glu Ala Phe Asp Phe Thr Ala Trp Pro
2705 2710 2715 2720

Pro Ala Gly Ala Gln Gln Val Asp Gly Leu Trp Arg Arg Gly Asp Glu
2725 2730 2735

Ile Phe Ala Glu Val Ala Leu Pro Glu Glu Leu Asp Ala Gly Ala Phe
2740 2745 2750

Gly Ile His Pro Phe Leu Leu Asp Ala Ala Val Gln Pro Val Leu Ala
2755 2760 2765

Asp Asp Glu Gln Pro Ala Glu Trp Arg Ser Leu Val Leu His Ala Ala
2770 2775 2780

Gly Ala Ser Ala Leu Arg Val Arg Leu Val Pro Gly Gly Ala Leu Gln
2785 2790 2795 2800

Ala Ala Asp Glu Thr Gly Gly Leu Val Leu Thr Ala Asp Ser Val Ala
2805 2810 2815

Gly Arg Glu Leu Ser Ala Gly Lys Thr Arg Ala Gly Ser Leu Tyr Arg
2820 2825 2830

Val Asp Trp Thr Glu Val Ser Ile Ala Asp Ser Ala Val Pro Ala Asn
2835 2840 2845

Ile Glu Val Val Glu Ala Phe Gly Glu Glu Pro Leu Glu Leu Thr Gly
2850 2855 2860

Arg Val Leu Glu Ala Val Gln Thr Trp Leu Val Thr Ala Ala Asp Asp
2865 2870 2875 2880

Ala Arg Leu Val Val Val Thr Arg Gly Ala Val Arg Glu Val Thr Asp
2885 2890 2895

Pro Ala Gly Ala Ala Val Trp Gly Leu Val Arg Ala Ala Gln Ala Glu
2900 2905 2910

Asn Pro Gly Arg Ile Phe Leu Ile Asp Thr Asp Gly Glu Ile Pro Ala

2915 2920 2925

Leu Thr Gly Asp Glu Pro Glu Ile Ala Val Arg Gly Gly Lys Phe Phe
2930 2935 2940

Val Pro Arg Ile Thr Arg Ala Glu Pro Ser Gly Ala Ala Val Phe Arg
2945 2950 2955 2960

Pro Asp Gly Thr Val Leu Ile Ser Gly Ala Gly Ala Leu Gly Gly Leu
2965 2970 2975

Val Ala Arg Arg Leu Val Glu Arg His Gly Val Arg Lys Leu Val Leu
2980 2985 2990

Ala Ser Arg Arg Gly Arg Asp Ala Asp Gly Val Ala Asp Leu Val Ala
2995 3000 3005

Asp Leu Ala Ala Asp Val Ser Val Val Ala Cys Asp Val Ser Asp Arg
3010 3015 3020

Ala Gln Val Ala Ala Leu Leu Asp Glu His Arg Pro Thr Ala Val Val
3025 3030 3035 3040

His Thr Ala Gly Val Ile Asp Ala Gly Val Ile Glu Thr Leu Asp Arg
3045 3050 3055

Asp Arg Leu Ala Thr Val Phe Ala Pro Lys Val Asp Ala Val Arg His
3060 3065 3070

Leu Asp Glu Leu Thr Arg Asp Arg Asp Leu Asp Ala Phe Val Val Tyr
3075 3080 3085

Ser Ser Val Ser Ala Val Phe Met Gly Ala Gly Ser Gly Ser Tyr Ala
3090 3095 3100

Ala Ala Asn Ala Phe Leu Asp Gly Leu Met Ala Asn Arg Arg Ala Ala
3105 3110 3115 3120

Gly Leu Pro Gly Leu Ser Leu Ala Trp Gly Leu Trp Asp Gln Ser Thr
3125 3130 3135

Gly Met Ala Ala Gly Thr Asp Glu Ala Thr Arg Ala Arg Met Ser Arg
3140 3145 3150

Arg Gly Gly Leu Gln Ile Met Thr Gln Ala Glu Gly Met Asp Leu Phe
3155 3160 3165

Asp Ala Ala Leu Ser Ser Ala Glu Ser Leu Leu Val Pro Ala Lys Leu
3170 3175 3180

Asp Leu Arg Gly Val Arg Ala Asp Ala Ala Ala Gly Gly Val Val Pro
3185 3190 3195 3200

His Met Leu Arg Gly Leu Val Arg Ala Gly Arg Ala Gln Ala Arg Ala
3205 3210 3215

Ala Ser Thr Val Asp Asn Gly Leu Ala Gly Arg Leu Ala Gly Leu Ala
3220 3225 3230

Pro Ala Asp Gln Leu Thr Leu Leu Leu Asp Leu Val Arg Ala Gln Val
3235 3240 3245

Ala Ala Val Leu Gly His Ala Asp Ala Ser Ala Val Arg Val Asp Thr
3250 3255 3260

Ala Phe Lys Asp Ala Gly Phe Asp Ser Leu Thr Ala Val Glu Leu Arg
3265 3270 3275 3280

Asn Arg Met Arg Thr Ala Thr Gly Leu Lys Leu Pro Ala Thr Leu Val
3285 3290 3295

Phe Asp Tyr Pro Asn Pro Gln Ala Leu Ala Arg His Leu Arg Asp Glu
3300 3305 3310

Leu Gly Gly Ala Ala Gln Thr Pro Val Thr Thr Ala Ala Ala Lys Ala
3315 3320 3325

Asp Leu Asp Glu Pro Ile Ala Ile Val Gly Met Ala Cys Arg Leu Pro
3330 3335 3340

Gly Gly Val Ala Gly Pro Glu Asp Leu Trp Arg Leu Val Ala Glu Gly
3345 3350 3355 3360

Arg Asp Ala Val Ser Ser Phe Pro Thr Asp Arg Gly Trp Asp Thr Asp
3365 3370 3375

Ser Leu Tyr Asp Pro Asp Pro Ala Arg Pro Gly Lys Thr Tyr Thr Arg
3380 3385 3390

His Gly Gly Phe Leu His Glu Ala Gly Leu Phe Asp Ala Gly Phe Phe
3395 3400 3405

Gly Ile Ser Pro Arg Glu Ala Val Ala Met Asp Pro Gln Gln Arg Leu
3410 3415 3420

Leu Leu Glu Ala Ser Trp Glu Ala Met Glu Asp Ala Gly Val Asp Pro
3425 3430 3435 3440

Leu Ser Leu Lys Gly Asn Asp Val Gly Val Phe Thr Gly Met Phe Gly
3445 3450 3455

Gln Gly Tyr Val Ala Pro Gly Asp Ser Val Val Thr Pro Glu Leu Glu
3460 3465 3470

Gly Phe Ala Gly Thr Gly Gly Ser Ser Ser Val Ala Ser Gly Arg Val
3475 3480 3485

Ser Tyr Val Phe Gly Phe Glu Gly Pro Ala Val Thr Ile Asp Ser Ala
3490 3495 3500

Cys Ser Ser Ser Leu Val Ala Met His Leu Ala Ala Gln Ser Leu Arg

3505 3510 3515 3520

Gln Gly Glu Cys Ser Met Ala Leu Ala Gly Gly Ala Thr Val Met Ala
3525 3530 3535

Asn Pro Gly Ala Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala Val
3540 3545 3550

Asp Gly Arg Cys Lys Ala Phe Ala Ala Ala Ala Asp Gly Thr Gly Trp
3555 3560 3565

Ala Glu Gly Val Gly Val Val Ile Leu Glu Arg Leu Ser Val Ala Arg
3570 3575 3580

Glu Arg Gly His Arg Ile Leu Ala Val Leu Arg Gly Ser Ala Val Asn
3585 3590 3595 3600

Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser Gln
3605 3610 3615

Gln Arg Val Ile Arg Arg Ala Leu Val Ser Ala Gly Leu Ala Pro Ser
3620 3625 3630

Asp Val Asp Val Val Glu Ala His Gly Thr Gly Thr Thr Leu Gly Asp
3635 3640 3645

Pro Ile Glu Ala Gln Ala Leu Leu Ala Thr Tyr Gly Lys Asp Arg Glu
3650 3655 3660

Ser Pro Leu Trp Leu Gly Ser Leu Lys Ser Asn Ile Gly His Ala Gln
3665 3670 3675 3680

Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Gln Ala Leu Arg
3685 3690 3695

His Glu Val Leu Pro Pro Thr Leu His Val Asp Arg Pro Thr Pro Glu
3700 3705 3710

Val Asp Trp Ser Ala Gly Ala Val Glu Leu Leu Thr Glu Ala Arg Glu
3715 3720 3725

Trp Pro Arg Asn Gly Arg Pro Arg Arg Ala Gly Val Ser Ala Phe Gly
3730 3735 3740

Val Ser Gly Thr Asn Ala His Leu Ile Leu Glu Glu Ala Pro Ala Glu
3745 3750 3755 3760

Glu Pro Val Pro Thr Pro Glu Val Pro Leu Val Pro Val Val Val Ser
3765 3770 3775

Ala Arg Ser Arg Ala Ser Leu Ala Gly Gln Ala Gly Arg Leu Ala Gly
3780 3785 3790

Phe Val Ala Gly Asp Ala Ser Leu Ala Gly Val Ala Arg Ala Leu Val
3795 3800 3805

Thr Asn Arg Ala Ala Leu Thr Glu Arg Ala Val Met Val Val Gly Ser
3810 3815 3820

Arg Glu Glu Ala Val Thr Asn Leu Glu Ala Leu Ala Arg Gly Glu Asp
3825 3830 3835 3840

Pro Ala Ala Val Val Thr Gly Arg Ala Gly Ser Pro Gly Lys Leu Val
3845 3850 3855

Trp Val Phe Pro Gly Gln Gly Ser Gln Trp Ile Gly Met Gly Arg Glu
3860 3865 3870

Leu Leu Asp Ser Ser Pro Val Phe Ala Glu Arg Val Ala Glu Cys Ala
3875 3880 3885

Ala Ala Leu Glu Pro Trp Ile Asp Trp Ser Leu Leu Asp Val Leu Arg
3890 3895 3900

Gly Glu Ser Asp Leu Leu Asp Arg Val Asp Val Val Gln Pro Ala Ser
3905 3910 3915 3920

Phe Ala Met Met Val Gly Leu Ala Ala Val Trp Gln Ser Val Gly Val
3925 3930 3935

Arg Pro Asp Ala Val Val Gly His Ser Gln Gly Glu Ile Ala Ala Ala
3940 3945 3950

Cys Val Ser Gly Ala Leu Ser Leu Gln Asp Ala Ala Lys Val Val Ala
3955 3960 3965

Leu Arg Ser Gln Ala Ile Ala Thr Arg Leu Ala Gly Arg Gly Gly Met
3970 3975 3980

Ala Ser Val Ala Leu Ser Glu Glu Asp Ala Thr Ala Trp Leu Ala Pro
3985 3990 3995 4000

Trp Ala Asp Arg Val Gln Val Ala Ala Val Asn Ser Pro Ala Ser Val
4005 4010 4015

Val Ile Ala Gly Glu Ala Gln Ala Leu Asp Glu Val Val Asp Ala Leu
4020 4025 4030

Ser Gly Gln Glu Val Arg Val Arg Arg Val Ala Val Asp Tyr Gly Ser
4035 4040 4045

His Thr Asn Gln Val Glu Ala Ile Glu Asp Leu Leu Ala Glu Thr Leu
4050 4055 4060

Ala Gly Ile Glu Ala Gln Ala Pro Lys Val Pro Phe Tyr Ser Thr Leu
4065 4070 4075 4080

Ile Gly Asp Trp Ile Arg Asp Ala Gly Ile Val Asp Gly Gly Tyr Trp
4085 4090 4095

Tyr Arg Asn Leu Arg Asn Gln Val Gly Phe Gly Pro Ala Val Ala Glu

4100 4105 4110

Leu Val Arg Gln Gly His Gly Val Phe Val Glu Val Ser Ala His Pro
4115 4120 4125

Val Leu Val Gln Pro Leu Ser Glu Leu Ser Asp Asp Ala Val Val Thr
4130 4135 4140

Gly Ser Leu Arg Arg Glu Asp Gly Gly Leu Arg Arg Leu Leu Thr Ser
4145 4150 4155 4160

Met Ala Glu Leu Tyr Val Gln Gly Val Pro Leu Asp Trp Thr Ala Val
4165 4170 4175

Leu Pro Arg Thr Gly Arg Val Asp Leu Pro Lys Tyr Ala Phe Asp His
4180 4185 4190

Arg His Tyr Trp Leu Arg Pro Ala Glu Ser Ala Thr Asp Ala Ala Ser
4195 4200 4205

Leu Gly Gln Ala Ala Ala Asp His Pro Leu Leu Gly Ala Val Val Glu
4210 4215 4220

Leu Pro Gln Ser Asp Gly Leu Val Phe Thr Ser Arg Leu Ser Val Arg
4225 4230 4235 4240

Thr His Pro Trp Leu Ala Asp His Ala Val Gly Gly Val Val Ile Leu
4245 4250 4255

Pro Gly Ser Gly Leu Ala Glu Leu Ala Val Arg Ala Gly Asp Glu Ala
4260 4265 4270

Gly Cys Thr Ala Leu Asp Glu Leu Ile Ile Glu Ala Pro Leu Val Val
4275 4280 4285

Pro Ala Gln Gly Ala Val Arg Val Gln Val Ala Leu Ser Gly Pro Asp
4290 4295 4300

Glu Thr Gly Ser Arg Thr Val Asp Leu Tyr Ser Gln Arg Asp Gly Gly
4305 4310 4315 4320

Ala Gly Thr Trp Thr Arg His Ala Thr Gly Val Leu Ser Thr Ala Pro
4325 4330 4335

Ala Gln Glu Pro Glu Phe Asp Phe His Ala Trp Pro Pro Ala Asp Ala
4340 4345 4350

Glu Arg Ile Asp Val Glu Thr Phe Tyr Thr Asp Leu Ala Glu Arg Gly
4355 4360 4365

Tyr Gly Tyr Gly Pro Ala Phe Gln Gly Leu Gln Ala Val Trp Arg Arg
4370 4375 4380

Asp Gly Asp Val Phe Ala Glu Val Ala Leu Pro Glu Asp Leu Arg Lys
4385 4390 4395 4400

Asp Ala Gly Arg Phe Gly Val His Pro Ala Leu Leu Asp Ala Ala Leu
4405 4410 4415

Gln Ala Ala Thr Ala Val Gly Gly Asp Glu Pro Gly Gln Pro Val Leu
4420 4425 4430

Ala Phe Ala Trp Asn Gly Leu Val Leu His Ala Ala Gly Ala Ser Ala
4435 4440 4445

Leu Arg Val Arg Leu Ala Pro Ser Gly Pro Asp Thr Leu Ser Val Ala
4450 4455 4460

Ala Ala Asp Glu Thr Gly Gly Leu Val Leu Thr Met Glu Ser Leu Val
4465 4470 4475 4480

Ser Arg Pro Val Ser Ala Glu Gln Leu Gly Ala Ala Ala Asp Ala Gly
4485 4490 4495

His Asp Ala Met Phe Arg Val Asp Trp Thr Glu Leu Pro Ala Val Pro
4500 4505 4510

Arg Ala Glu Leu Pro Pro Trp Val Arg Ile Asp Thr Ala Asp Asp Val
4515 4520 4525

Ala Ala Leu Ala Glu Lys Ala Asp Ala Pro Pro Val Val Val Trp Glu
4530 4535 4540

Ala Ala Gly Gly Asp Pro Ala Leu Ala Val Ser Ser Arg Val Leu Glu
4545 4550 4555 4560

Ile Met Gln Ala Trp Leu Ala Ala Pro Ala Phe Glu Glu Ala Arg Leu
4565 4570 4575

Val Val Thr Thr Arg Gly Ala Val Pro Ala Gly Gly Asp His Thr Leu
4580 4585 4590

Thr Asp Pro Ala Ala Ala Ala Val Trp Gly Leu Val Arg Ser Ala Gln
4595 4600 4605

Ala Glu His Pro Asp Arg Val Val Leu Leu Asp Thr Asp Gly Glu Val
4610 4615 4620

Pro Leu Gly Ala Val Leu Ala Ser Gly Glu Pro Gln Leu Ala Val Arg
4625 4630 4635 4640

Gly Thr Thr Phe Phe Val Pro Arg Leu Ala Arg Ala Thr Arg Leu Ser
4645 4650 4655

Asp Ala Pro Pro Ala Phe Asp Pro Asp Gly Thr Val Leu Val Ser Gly
4660 4665 4670

Ala Gly Ser Leu Gly Thr Leu Val Ala Arg His Leu Val Thr Arg His
4675 4680 4685

Gly Val Arg Arg Val Val Leu Ala Ser Arg Gln Gly Arg Asp Ala Glu

4690 4695 4700

Gly Ala Gln Asp Leu Ile Thr Glu Leu Thr Gly Glu Gly Ala Asp Val
4705 4710 4715 4720

Ser Phe Val Ala Cys Asp Val Ser Asp Arg Asp Gln Val Ala Ala Leu
4725 4730 4735

Leu Ala Gly Leu Pro Asp Leu Thr Gly Val Val His Thr Ala Gly Val
4740 4745 4750

Phe Glu Asp Gly Val Ile Glu Ala Leu Thr Pro Asp Gln Leu Ala Asn
4755 4760 4765

Val Tyr Ala Ala Lys Val Thr Ala Ala Met His Leu Asp Glu Leu Thr
4770 4775 4780

Arg Asp Arg Asp Leu Gly Ala Phe Val Val Phe Ser Ser Val Ala Gly
4785 4790 4795 4800

Val Met Gly Gly Gly Gly Gln Gly Pro Tyr Ala Ala Ala Asn Ala Phe
4805 4810 4815

Leu Asp Ala Ala Met Ala Ser Arg Gln Ala Ala Gly Leu Pro Gly Leu
4820 4825 4830

Ser Leu Ala Trp Gly Leu Trp Glu Arg Ser Ser Gly Met Ala Ala His
4835 4840 4845

Leu Ser Glu Val Asp His Ala Arg Ala Ser Arg Asn Gly Val Leu Glu
4850 4855 4860

Leu Thr Arg Ala Glu Gly Leu Ala Leu Phe Asp Leu Gly Leu Arg Met
4865 4870 4875 4880

Ala Glu Ser Leu Leu Val Pro Ile Lys Leu Asp Leu Ala Ala Met Arg
4885 4890 4895

Ala Ser Thr Val Pro Val Leu Phe Arg Gly Leu Val Arg Pro Ser Arg
4900 4905 4910

Thr Gln Ala Arg Thr Ala Ser Thr Val Asp Arg Gly Leu Ala Gly Arg
4915 4920 4925

Leu Ala Gly Leu Pro Val Ala Glu Arg Ala Ala Val Leu Val Asp Leu
4930 4935 4940

Val Arg Gly Gln Val Ala Val Val Leu Gly Tyr Asp Gly Pro Glu Ala
4945 4950 4955 4960

Val Arg Pro Asp Thr Ala Phe Lys Asp Thr Gly Phe Asp Ser Leu Thr
4965 4970 4975

Ser Val Glu Leu Arg Asn Arg Leu Arg Glu Ala Thr Gly Leu Lys Leu
4980 4985 4990

Pro Ala Thr Leu Val Phe Asp Tyr Pro Asn Pro Leu Ala Val Ala Arg
4995 5000 5005

Tyr Leu Gly Ala Arg Leu Val Pro Asp Gly Thr Ala Asn Gly Asn Gly
5010 5015 5020

Asn Gly Asn Gly His Ser Glu Asp Asp Arg Leu Arg His Ala Leu Ala
5025 5030 5035 5040

Ala Ile Ala Ala Glu Asp Ala Gly Glu Glu Arg Ser Ile Ala Asp Leu
5045 5050 5055

Gly Val Asp Asp Leu Val Gln Leu Ala Phe Gly Asp Glu
5060 5065

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1721 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Met Ala Cys Arg Leu Pro Gly Gly Val Thr Gly Pro Gly Asp Leu Trp
1   5   10   15

Arg Leu Val Ala Glu Gly Gly Asp Ala Val Ser Gly Phe Pro Thr Asp
            20   25   30

Arg Cys Trp Asp Leu Asp Thr Leu Phe Asp Pro Asp Pro Asp His Ala
        35   40   45

Gly Thr Ser Tyr Thr Asp Gln Gly Gly Phe Leu His Asp Ala Ala Leu
    50   55   60

Phe Asp Pro Gly Phe Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met
65   70   75   80

Asp Pro Gln Gln Arg Leu Leu Leu Glu Ala Ser Trp Glu Ala Leu Glu
                85   90   95

Gly Val Gly Leu Asp Pro Ala Ser Leu Gln Gly Thr Asp Val Gly Val
            100   105   110

Phe Thr Gly Ala Gly Gly Ser Gly Tyr Gly Gly Gly Leu Thr Gly Pro
        115   120   125

Glu Met Gln Ser Phe Ala Gly Thr Gly Leu Ala Ser Ser Val Ala Ser

130 135 140

Gly Arg Val Ser Tyr Val Phe Gly Phe Glu Gly Pro Ala Val Thr Ile
145 150 155 160

Asp Thr Ala Cys Ser Ser Ser Leu Val Ala Met His Leu Ala Ala Gln
165 170 175

Ala Leu Arg Gln Gly Asp Cys Ser Met Ala Leu Ala Gly Gly Ala Met
180 185 190

Val Met Ser Gly Pro Asp Ser Phe Val Val Phe Ser Arg Gln Arg Gly
195 200 205

Leu Ala Thr Asp Gly Arg Cys Lys Ala Phe Ala Ser Gly Ala Asp Gly
210 215 220

Met Val Leu Ala Glu Gly Ile Ser Val Val Val Leu Glu Arg Leu Ser
225 230 235 240

Val Ala Arg Glu Arg Gly His Arg Val Leu Ala Val Leu Arg Gly Ser
245 250 255

Ala Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly
260 265 270

Pro Ser Gln Gln Arg Val Ile Arg Ala Ala Leu Ala Asn Ala Gly Ile
275 280 285

Gly Pro Ser Asp Val Asp Leu Val Glu Ala His Gly Thr Gly Thr Ser
290 295 300

Leu Gly Asp Pro Ile Glu Ala Gln Ala Leu Leu Ala Thr Tyr Gly Gln
305 310 315 320

Asp Arg Glu Thr Pro Leu Trp Leu Gly Ser Leu Lys Ser Asn Ile Gly
325 330 335

His Thr Gln Ala Ala Ala Gly Val Ala Ser Val Ile Lys Val Val Gln
340 345 350

Ala Leu Arg His Gly Val Met Pro Pro Thr Leu His Val Asp Glu Pro
355 360 365

Ser Ser Gln Val Asp Trp Ser Glu Gly Ala Val Glu Leu Leu Thr Gly
370 375 380

Ser Arg Asp Trp Pro Arg Gly Asp Arg Pro Arg Arg Ala Gly Val Ser
385 390 395 400

Ser Phe Gly Val Ser Gly Thr Asn Val His Leu Ile Ile Glu Glu Ala
405 410 415

Pro Glu Glu Pro Ala Ala Ala Val Pro Thr Ser Ala Asp Val Val Pro
420 425 430

Leu Val Val Ser Ala Arg Ser Thr Gly Ser Leu Ala Gly Gln Ala Asp
435 440 445

Arg Leu Thr Glu Val Asp Val Pro Leu Gly His Leu Ala Gly Ala Leu
450 455 460

Val Ala Gly Arg Ala Val Leu Glu Glu Arg Ala Val Val Val Ala Gly
465 470 475 480

Ser Ala Glu Glu Ala Arg Ala Gly Leu Gly Ala Leu Ala Arg Gly Glu
485 490 495

Ala Ala Pro Gly Val Val Thr Gly Thr Ala Gly Lys Pro Gly Lys Val
500 505 510

Val Trp Val Phe Pro Gly Gln Gly Thr Gln Trp Val Gly Met Gly Arg
515 520 525

Glu Leu Leu Asp Ala Ser Pro Val Phe Ala Glu Arg Ile Lys Glu Cys
530 535 540

Ala Ala Ala Leu Asp Gln Trp Thr Asp Trp Ser Leu Leu Asp Val Leu
545 550 555 560

Arg Gly Asp Gly Asp Leu Asp Ser Val Glu Val Leu Gln Pro Ala Cys
565 570 575

Phe Ala Val Met Val Gly Leu Ala Ala Val Trp Glu Ser Ala Gly Val
580 585 590

Arg Pro Asp Ala Val Val Gly His Ser Gln Gly Glu Ile Ala Ala Ala
595 600 605

Cys Val Ser Gly Ala Leu Thr Leu Asp Asp Ala Ala Lys Val Val Ala
610 615 620

Leu Arg Ser Gln Ala Ile Ala Ala Arg Leu Ser Gly Arg Gly Gly Met
625 630 635 640

Ala Ser Val Ala Leu Ser Glu Asp Glu Ala Asn Ala Arg Leu Gly Leu
645 650 655

Trp Asp Gly Arg Ile Glu Val Ala Ala Val Asn Gly Pro Ala Ser Val
660 665 670

Val Ile Ala Gly Asp Ala Gln Ala Leu Asp Glu Ala Leu Glu Val Leu
675 680 685

Ala Gly Asp Gly Val Arg Val Arg Gln Val Ala Val Asp Tyr Ala Ser
690 695 700

His Thr Arg His Val Glu Asp Ile Arg Asp Thr Leu Ala Glu Thr Leu
705 710 715 720

Ala Gly Ile Thr Ala Gln Ala Pro Asp Val Pro Phe Arg Ser Thr Val

725 730 735

Thr Gly Gly Trp Val Arg Asp Ala Asp Val Leu Asp Gly Gly Tyr Trp
740 745 750

Tyr Arg Asn Leu Arg Asn Gln Val Arg Phe Gly Pro Ala Val Ala Glu
755 760 765

Leu Leu Glu Gln Gly His Gly Val Phe Val Glu Val Ser Ala His Pro
770 775 780

Val Leu Val Gln Pro Ile Ser Glu Leu Thr Asp Ala Val Val Thr Gly
785 790 795 800

Thr Leu Arg Arg Asp Asp Gly Gly Leu Arg Arg Leu Leu Thr Ser Met
805 810 815

Ala Glu Leu Phe Val Arg Gly Val Arg Val Asp Trp Ala Thr Leu Val
820 825 830

Pro Pro Ala Arg Val Asp Leu Pro Thr Tyr Ala Phe Asp His Gln His
835 840 845

Phe Trp Leu Arg Pro Ala Ala Gln Ala Asp Ala Val Ser Leu Gly Gln
850 855 860

Ala Ala Ala Glu His Pro Leu Leu Gly Ala Val Val Arg Leu Pro Gln
865 870 875 880

Ser Asp Gly Leu Val Phe Thr Ser Arg Leu Ser Leu Arg Thr His Pro
885 890 895

Trp Leu Ala Asp His Thr Ile Gly Gly Val Val Leu Phe Pro Gly Thr
900 905 910

Gly Leu Val Glu Leu Ala Val Arg Ala Gly Asp Glu Ala Gly Cys Pro
915 920 925

Val Leu Asp Glu Leu Val Thr Glu Ala Pro Leu Val Val Pro Gly Gln
930 935 940

Gly Gly Val Asn Val Gln Val Thr Val Ser Gly Pro Asp Gln Asn Gly
945 950 955 960

Leu Arg Thr Val Asp Ile His Ser Gln Arg Asp Asp Val Trp Thr Arg
965 970 975

His Ala Thr Gly Thr Val Ser Ala Thr Pro Ala Ser Ser Pro Gly Phe
980 985 990

Asp Phe Thr Ala Trp Pro Pro Pro Asp Gly Gln Arg Val Glu Ile Gly
995 1000 1005

Asp Phe Tyr Ala Asp Leu Ala Glu Arg Gly Tyr Ala Tyr Gly Pro Leu
1010 1015 1020

Phe Gln Gly Val Arg Ala Val Trp Gln Arg Gly Glu Asp Val Phe Ala
1025 1030 1035 1040

Glu Val Ala Leu Pro Glu Asp Arg Arg Glu Asp Ala Ala Arg Phe Gly
1045 1050 1055

Leu His Pro Ala Leu Leu Asp Ala Ala Leu Gln Thr Gly Thr Ile Ala
1060 1065 1070

Ala Ala Ala Ser Gly Gln Pro Gly Lys Ser Val Met Pro Phe Ser Trp
1075 1080 1085

Asn Arg Leu Ala Leu His Ala Val Gly Ala Ala Gly Leu Arg Val Arg
1090 1095 1100

Val Ala Pro Gly Gly Pro Asp Ala Leu Thr Val Glu Ala Ala Asp Glu
1105 1110 1115 1120

Thr Gly Ala Pro Val Leu Thr Met Asp Ser Leu Ile Leu Arg Glu Val
1125 1130 1135

Ala Leu Asp Gln Leu Asp Thr Ala Arg Ala Gly Ser Leu Tyr Arg Val
1140 1145 1150

Asp Trp Thr Pro Leu Pro Thr Val Asp Ser Ala Val Pro Ala Gly Arg
1155 1160 1165

Ala Glu Val Leu Glu Ala Phe Gly Glu Glu Pro Leu Asp Leu Thr Gly
1170 1175 1180

Arg Val Leu Ala Ala Leu Gln Ala Trp Leu Ser Asp Ala Ala Glu Glu
1185 1190 1195 1200

Ala Arg Leu Val Val Val Thr Arg Gly Ala Val Pro Ala Gly Asp Gly
1205 1210 1215

Val Val Ser Asp Pro Ala Gly Ala Ala Val Trp Gly Leu Val Arg Ala
1220 1225 1230

Ala Gln Ala Glu Asn Pro Asp Arg Phe Val Leu Leu Asp Thr Asp Gly
1235 1240 1245

Glu Val Pro Leu Glu Ala Val Leu Ala Thr Gly Glu Pro Gln Leu Ala
1250 1255 1260

Leu Arg Gly Thr Thr Phe Ser Val Pro Arg Leu Ala Arg Val Thr Glu
1265 1270 1275 1280

Pro Ala Glu Ala Pro Leu Thr Phe Arg Pro Asp Gly Thr Val Leu Val
1285 1290 1295

Ser Gly Ala Gly Thr Leu Gly Ala Leu Ala Ala Arg Asp Leu Val Thr
1300 1305 1310

Arg His Gly Val Arg Arg Leu Val Leu Ala Ser Arg Arg Gly Arg Ala

1315 1320 1325

Ala Glu Gly Ile Asp Asp Leu Val Ala Glu Leu Thr Gly His Gly Ala
1330 1335 1340

Glu Val Thr Val Ala Ala Cys Asp Val Ser Asp Arg Asp Gln Val Ala
1345 1350 1355 1360

Ala Leu Leu Lys Glu His Ala Leu Thr Ala Val Val His Thr Ala Gly
1365 1370 1375

Val Phe Asp Ala Gly Val Thr Gly Ala Leu Thr Arg Glu Arg Leu Ala
1380 1385 1390

Lys Val Phe Ala Pro Lys Val Asp Ala Ala Asn His Leu Asp Glu Leu
1395 1400 1405

Thr Arg Asp Leu Asp Leu Asp Ala Phe Ile Val Tyr Ser Ser Ala Ser
1410 1415 1420

Ser Ile Phe Met Gly Ala Gly Ser Gly Gly Tyr Ala Ala Ala Asn Ala
1425 1430 1435 1440

Tyr Leu Asp Gly Leu Met Ala Ala Arg Arg Ala Ala Gly Leu Pro Gly
1445 1450 1455

Leu Ser Leu Ala Trp Gly Pro Trp Glu Gln Leu Thr Gly Met Ala Asp
1460 1465 1470

Thr Ile Asp Asp Leu Thr Leu Ala Arg Met Ser Arg Arg Glu Gly Arg
1475 1480 1485

Gly Gly Val Arg Ala Leu Gly Ser Ala Asp Gly Met Glu Leu Phe Asp
1490 1495 1500

Ala Ala Leu Ala Ala Gly Gln Ala Leu Leu Val Pro Ile Glu Leu Asp
1505 1510 1515 1520

Leu Arg Glu Val Arg Ala Asp Ala Ala Gly Gly Gly Thr Val Pro His
1525 1530 1535

Leu Leu Arg Gly Leu Val Arg Ala Gly Arg Gln Ala Ala Arg Thr Ala
1540 1545 1550

Ala Thr Glu Asp Gly Gly Leu Glu Arg Arg Leu Ala Gly Leu Thr Val
1555 1560 1565

Ala Glu Gln Glu Ala Leu Leu Leu Asp Leu Val Arg Gly Gln Val Ala
1570 1575 1580

Val Val Leu Gly His Ala Asp Ser Ser Gly Val Arg Ala Asp Ala Ala
1585 1590 1595 1600

Phe Lys Asp Ala Gly Phe Asp Ser Leu Thr Ser Val Glu Leu Arg Asn
1605 1610 1615

Arg Leu Arg Glu Thr Thr Gly Leu Lys Leu Pro Ala Thr Leu Val Phe
1620 1625 1630

Asp His Pro Asn Pro Leu Ala Leu Ala Arg His Leu Arg Ala Glu Leu
1635 1640 1645

Ala Val Asp Glu Ala Ser Pro Ala Asp Ala Val Leu Ala Gly Leu Ala
1650 1655 1660

Gly Leu Glu Ala Ala Ile Ala Ala Ala Gly Ala Pro Asp Gly Asp Arg
1665 1670 1675 1680

Ile Thr Ala Arg Leu Arg Glu Leu Leu Lys Ala Ala Glu Ala Ala Glu
1685 1690 1695

Ala Arg Pro Gly Thr Ser Gly Asp Leu Asp Thr Ala Ser Asp Glu Glu
1700 1705 1710

Leu Phe Ala Leu Val Asp Gly Leu Asp
1715 1720

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1688 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

Met Ala Cys Arg Tyr Pro Gly Gly Val Ser Ser Pro Glu Asp Leu Trp
1 5 10 15

Arg Leu Val Ala Glu Gly Thr Asp Ala Val Ser Ala Phe Pro Gly Asp
20 25 30

Arg Gly Trp Asp Val Asp Gly Leu Val Asp Pro Asp Pro Asp Arg Pro
35 40 45

Gly Thr Thr Tyr Thr Asp Gln Gly Gly Phe Leu His Glu Ala Gly Leu
50 55 60

Phe Asp Ala Gly Phe Phe Gly Ile Ser Pro Arg Glu Ala Val Ala Met
65 70 75 80

Asp Pro Gln Gln Arg Leu Leu Leu Glu Thr Ser Trp Glu Ala Ile Glu
85 90 95

Arg Thr Gly Thr Asp Pro Leu Ser Leu Lys Gly Ser Asp Ile Gly Val

100 105 110

Phe Thr Gly Val Ala Ser Met Gly Tyr Gly Ala Gly Gly Gly Val Val
115 120 125

Ala Pro Glu Leu Glu Gly Phe Val Gly Thr Gly Ala Ala Pro Cys Ile
130 135 140

Ala Ser Gly Arg Val Ser Tyr Val Leu Gly Phe Glu Gly Pro Ala Val
145 150 155 160

Thr Val Asp Thr Gly Cys Ser Ser Ser Leu Val Ala Met His Leu Ala
165 170 175

Ala Gln Ala Leu Arg Arg Gly Glu Cys Ser Met Ala Leu Ala Gly Gly
180 185 190

Ala Met Val Met Ala Gln Pro Gly Ser Phe Val Ser Phe Ser Arg Gln
195 200 205

Arg Gly Leu Ala Leu Asp Gly Arg Cys Lys Ala Phe Ser Asp Ser Ala
210 215 220

Asp Gly Met Gly Leu Ala Glu Gly Val Gly Val Ile Ala Leu Glu Arg
225 230 235 240

Leu Ser Val Ala Arg Glu Arg Gly His Arg Val Leu Ala Val Leu Arg
245 250 255

Gly Ile Ala Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro
260 265 270

Asn Gly Pro Ser Gln Gln Arg Val Ile Arg Ala Ala Leu Ala Glu Ala
275 280 285

Gly Leu Ser Pro Ser Asp Val Asp Ala Val Glu Gly His Gly Thr Gly
290 295 300

Thr Thr Leu Gly Asp Pro Ile Glu Ala Gln Ala Leu Leu Ala Thr Tyr
305 310 315 320

Gly Lys Gly Arg Asp Pro Glu Lys Pro Leu Trp Leu Gly Ser Val Lys
325 330 335

Ser Asn Leu Gly His Thr Gln Ala Ala Ala Gly Val Ala Ser Val Ile
340 345 350

Lys Met Val Gln Ala Leu Arg His Gly Val Leu Pro Pro Thr Leu His
355 360 365

Val Asp Arg Pro Ser Thr Glu Val Asp Trp Ser Ala Gly Ala Val Ser
370 375 380

Leu Leu Thr Glu Ala Arg Glu Trp Pro Arg Glu Gly Arg Pro Arg Arg
385 390 395 400

Ala Gly Val Ser Ser Phe Gly Ile Ser Gly Thr Asn Ala His Leu Ile
405 410 415

Leu Glu Glu Ala Pro Glu Glu Glu Pro Pro Val Ala Glu Ala Pro Ser
420 425 430

Ala Gly Val Val Pro Val Val Val Ser Ala Arg Gly Ala Leu Ala Gly
435 440 445

Gln Ala Gly Arg Leu Ala Ala Phe Leu Glu Ala Ser Asp Glu Pro Leu
450 455 460

Val Thr Val Ala Gly Ala Leu Ile Cys Gly Arg Ser Arg Phe Gly Asp
465 470 475 480

Arg Ala Val Val Val Ala Gly Thr Arg Ala Glu Ala Thr Ala Gly Leu
485 490 495

Ala Ala Leu Ala Arg Gly Glu Ser Ala Ala Asp Val Val Thr Gly Thr
500 505 510

Val Ala Ala Ser Gly Val Pro Gly Lys Leu Val Trp Val Phe Pro Gly
515 520 525

Gln Gly Ser Gln Trp Val Gly Met Gly Arg Glu Leu Leu Glu Ala Ser
530 535 540

Pro Val Phe Ala Ala Arg Ile Ala Glu Cys Ala Ala Ala Leu Glu Pro
545 550 555 560

Trp Ile Asp Trp Ser Leu Leu Asp Val Leu Arg Gly Glu Gly Asp Leu
565 570 575

Asp Arg Val Asp Val Val Gln Pro Ala Ser Phe Ala Val Met Val Gly
580 585 590

Leu Ala Ala Val Trp Ser Ser Val Gly Val Val Pro Asp Ala Val Leu
595 600 605

Gly His Ser Gln Gly Glu Ile Ala Ala Ala Cys Val Ser Gly Ala Leu
610 615 620

Ser Leu Gln Asp Ala Ala Lys Val Val Ala Leu Arg Ser Gln Ala Ile
625 630 635 640

Ala Ala Lys Leu Ala Gly Arg Gly Gly Met Ala Ser Val Ala Leu Ser
645 650 655

Glu Glu Asp Ala Val Ala Arg Leu Arg His Trp Ala Asp Arg Val Glu
660 665 670

Val Ala Ala Val Asn Ser Pro Ser Ser Val Val Ile Ala Gly Asp Ala
675 680 685

Glu Ala Leu Asp Gln Ala Leu Glu Ala Leu Thr Gly Gln Asp Ile Arg

690 695 700

Val Arg Arg Val Ala Val Asp Tyr Ala Ser His Thr Arg His Val Glu
705 710 715 720

Asp Ile Gln Glu Pro Leu Ala Glu Ala Leu Ala Gly Ile Glu Ala His
725 730 735

Ala Pro Thr Leu Pro Phe Phe Ser Thr Leu Thr Gly Asp Trp Ile Arg
740 745 750

Glu Ala Gly Val Val Asp Gly Gly Tyr Trp Tyr Arg Asn Leu Arg Asn
755 760 765

Gln Val Gly Phe Gly Pro Ala Val Ala Glu Leu Leu Gly Leu Gly His
770 775 780

Arg Val Phe Val Glu Val Ser Ala His Pro Val Leu Val Gln Ala Ile
785 790 795 800

Ser Ala Ile Ala Asp Asp Thr Asp Ala Val Val Thr Gly Ser Leu Arg
805 810 815

Arg Glu Glu Gly Gly Leu Arg Arg Leu Leu Thr Ser Met Ala Glu Leu
820 825 830

Phe Val Arg Gly Val Asp Val Asp Trp Ala Thr Met Val Pro Pro Ala
835 840 845

Arg Val Asp Leu Pro Thr Tyr Ala Phe Asp His Gln His Tyr Trp Leu
850 855 860

Arg Tyr Val Glu Thr Ala Thr Asp Ala Ala Gly Pro Val Val Arg Leu
865 870 875 880

Pro Gln Thr Gly Gly Leu Val Phe Thr Thr Glu Trp Ser Leu Lys Ser
885 890 895

Gln Pro Trp Leu Ala Glu His Thr Leu Glu Asp Leu Val Val Val Pro
900 905 910

Gly Ala Ala Leu Val Glu Leu Ala Val Arg Ala Gly Asp Glu Ala Gly
915 920 925

Thr Pro Val Leu Asp Glu Leu Val Ile Glu Thr Pro Leu Val Val Pro
930 935 940

Glu Arg Gly Ala Ile Arg Val Gln Val Thr Val Ser Gly Pro Asp Asp
945 950 955 960

Gly Thr Arg Thr Leu Glu Val His Ser Gln Pro Glu Asp Ala Thr Asp
965 970 975

Glu Trp Thr Arg His Ala Thr Gly Thr Leu Ser Ala Thr Pro Asp Glu
980 985 990

Ser Ser Gly Phe Asp Phe Thr Ala Trp Pro Pro Pro Gly Ala Arg Gln
995 1000 1005

Leu Asp Gly Val Pro Ala Ile Trp Arg Ala Gly Asp Glu Ile Phe Ala
1010 1015 1020

Glu Val Ser Leu Pro Asp Asp Ala Asp Ala Glu Ala Phe Gly Ile His
1025 1030 1035 1040

Pro Ala Leu Leu Asp Ala Ala Leu His Pro Ala Leu Pro Gly Asp Asp
1045 1050 1055

Gly Leu Thr Gln Pro Met Glu Trp Arg Gly Leu Thr Leu His Ala Ala
1060 1065 1070

Gly Ala Ser Thr Leu Arg Val Arg Leu Val Pro Gly Gly Phe Leu Glu
1075 1080 1085

Ala Ala Asp Gly Ala Gly Ser Leu Val Val Thr Ala Lys Glu Val Ala
1090 1095 1100

Leu Arg Pro Val Thr Ile Ala Arg Ser Arg Thr Thr Thr Arg Asp Ser
1105 1110 1115 1120

Leu Phe Gln Leu Asn Trp Ile Glu Leu Pro Glu Ser Gly Val Val Ala
1125 1130 1135

Ala Ala Asp Asp Thr Glu Val Leu Glu Val Pro Ala Gly Asp Ser Pro
1140 1145 1150

Leu Ala Ala Thr Ser Arg Val Leu Glu Arg Leu Gln Thr Trp Leu Thr
1155 1160 1165

Glu Pro Glu Ala Glu Gln Leu Val Val Val Thr Arg Gly Ala Val Pro
1170 1175 1180

Ala Gly Asp Thr Pro Val Thr Asp Pro Ala Ala Ala Ala Val Trp Gly
1185 1190 1195 1200

Leu Val Arg Ser Ala Gln Ala Glu Asn Pro Asp Arg Ile Val Leu Leu
1205 1210 1215

Asp Thr Asp Gly Glu Val Pro Leu Gly Ala Val Leu Ala Gly Gly Glu
1220 1225 1230

Pro Gln Val Ala Val Arg Gly Thr Ala Leu Tyr Val Pro Arg Leu Ala
1235 1240 1245

Arg Ala Asp Ala Ala Pro Val Ser Gly Leu His Gly Thr Val Leu Val
1250 1255 1260

Ser Gly Ala Gly Val Leu Gly Glu Ile Val Ala Arg His Leu Val Thr
1265 1270 1275 1280

Arg His Gly Val Arg Lys Leu Val Leu Ala Ser Arg Arg Gly Leu Asp

1285 1290 1295

Ala Asp Gly Ala Lys Asp Leu Val Thr Asp Leu Thr Gly Glu Gly Ala
1300 1305 1310

Asp Val Ser Val Val Ala Cys Asp Leu Ala Asp Arg Asn Gln Val Ala
1315 1320 1325

Ala Leu Leu Ala Asp His Arg Pro Ala Ser Val Ile His Thr Ala Gly
1330 1335 1340

Val Leu Asp Asp Gly Val Ile Gly Thr Leu Thr Pro Glu Arg Leu Ala
1345 1350 1355 1360

Lys Val Phe Ala Pro Lys Val Asp Ala Val Arg His Leu Asp Glu Leu
1365 1370 1375

Thr Arg Asp Leu Asp Leu Asp Ala Phe Val Val Phe Ser Ser Gly Ser
1380 1385 1390

Gly Val Phe Gly Ser Pro Gly Gln Gly Asn Tyr Ala Ala Ala Asn Ala
1395 1400 1405

Phe Leu Asp Ala Ala Met Ala Ser Arg Arg Ala Ala Gly Leu Pro Gly
1410 1415 1420

Leu Ser Leu Ala Trp Gly Leu Trp Glu Gln Ala Thr Gly Met Thr Ala
1425 1430 1435 1440

His Leu Gly Gly Thr Asp Gln Ala Arg Met Ser Arg Gly Gly Val Arg
1445 1450 1455

Pro Ile Thr Ala Glu Glu Gly Met Ala Leu Phe Asp Thr Ala Leu Gly
1460 1465 1470

Ala Gln Pro Ala Leu Leu Val Pro Val Lys Leu Asp Leu Arg Glu Val
1475 1480 1485

Arg Ala Gly Gly Ala Val Pro His Leu Leu Arg Gly Leu Val Arg Ala
1490 1495 1500

Gly Arg Arg Gln Ala Gln Ala Ala Ser Thr Val Asp Asn Gln Leu Leu
1505 1510 1515 1520

Gly Arg Leu Ala Gly Leu Gly Ala Pro Glu Gln Glu Ala Leu Leu Val
1525 1530 1535

Asp Leu Val Arg Gly Gln Val Ala Ala Val Leu Gly His Ala Gly Pro
1540 1545 1550

Asp Ala Val Arg Ala Asp Thr Ala Phe Lys Asp Ala Gly Phe Asp Ser
1555 1560 1565

Leu Thr Ser Val Asp Leu Arg Asn Arg Leu Arg Glu Ser Thr Gly Leu
1570 1575 1580

Lys Leu Pro Ala Thr Leu Ala Phe Asp Tyr Pro Thr Pro Leu Val Leu
1585 1590 1595 1600

Ala Arg His Leu Arg Asp Glu Leu Gly Ala Gly Asp Asp Ala Leu Ser
1605 1610 1615

Val Val His Ala Arg Leu Glu Asp Val Glu Ala Leu Leu Gly Gly Leu
1620 1625 1630

Arg Leu Asp Glu Ser Thr Lys Thr Gly Leu Thr Leu Arg Leu Gln Gly
1635 1640 1645

Leu Val Ala Arg Cys Asn Gly Val Asn Asp Gln Thr Gly Gly Glu Thr
1650 1655 1660

Leu Ala Asp Arg Leu Glu Ala Ala Ser Ala Asp Glu Val Leu Asp Phe
1665 1670 1675 1680

Ile Asp Glu Glu Leu Gly Leu Thr
1685

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3413 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Met Ala Thr Asp Glu Lys Leu Leu Lys Tyr Leu Lys Arg Val Thr Ala
1 5 10 15

Glu Leu His Ser Leu Arg Lys Gln Gly Ala Arg His Ala Asp Glu Pro
20 25 30

Leu Ala Val Val Gly Met Ala Cys Arg Phe Pro Gly Gly Val Ser Ser
35 40 45

Pro Glu Asp Leu Trp Gln Leu Val Ala Gly Gly Val Asp Ala Leu Ser
50 55 60

Asp Phe Pro Asp Asp Arg Gly Trp Glu Leu Asp Gly Leu Phe Asp Pro
65 70 75 80

Asp Pro Asp His Pro Gly Thr Ser Tyr Thr Ser Gln Gly Gly Phe Leu
85 90 95

Arg Gly Ala Gly Leu Phe Asp Ala Gly Leu Phe Gly Ile Ser Pro Arg

100 105 110

Glu Ala Leu Val Met Asp Pro Gln Gln Arg Val Leu Leu Glu Thr Ser
115 120 125

Trp Glu Ala Leu Glu Asp Ala Gly Val Asp Pro Leu Ser Leu Lys Gly
130 135 140

Ser Asp Val Gly Val Phe Ser Gly Val Phe Thr Gln Gly Tyr Gly Ala
145 150 155 160

Gly Ala Ile Thr Pro Asp Leu Glu Ala Phe Ala Gly Ile Gly Ala Ala
165 170 175

Ser Ser Val Ala Ser Gly Arg Val Ser Tyr Val Phe Gly Leu Glu Gly
180 185 190

Pro Ala Val Thr Ile Asp Thr Ala Cys Ser Ser Ser Leu Val Ala Ile
195 200 205

His Leu Ala Ala Gln Ala Leu Arg Ala Gly Glu Cys Ser Met Ala Leu
210 215 220

Ala Gly Gly Ala Thr Val Met Pro Thr Pro Gly Thr Phe Val Ala Phe
225 230 235 240

Ser Arg Gln Arg Val Leu Ala Ala Asp Gly Arg Ser Lys Ala Phe Ser
245 250 255

Ser Thr Ala Asp Gly Thr Gly Trp Ala Glu Gly Ala Gly Val Leu Val
260 265 270

Leu Glu Arg Leu Ser Val Ala Gln Glu Arg Gly His Arg Ile Leu Ala
275 280 285

Val Leu Arg Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly Leu
290 295 300

Thr Ala Pro Asn Gly Pro Ser Gln Gln Arg Val Ile Arg Lys Ala Leu
305 310 315 320

Ala Gly Ala Gly Leu Val Ala Ser Asp Val Asp Val Val Glu Ala His
325 330 335

Gly Thr Gly Thr Ala Leu Gly Asp Pro Ile Glu Ala Gln Ala Leu Leu
340 345 350

Ala Thr Tyr Gly Gln Gly Arg Glu Arg Pro Leu Trp Leu Gly Ser Val
355 360 365

Lys Ser Asn Phe Gly His Thr Gln Ala Ala Ala Gly Val Ala Gly Val
370 375 380

Ile Lys Met Val Gln Ala Leu Arg His Gly Ala Met Pro Pro Thr Leu
385 390 395 400

His Val Ala Glu Pro Thr Pro Glu Val Asp Trp Ser Ala Gly Ala Val
405 410 415

Glu Leu Leu Thr Glu Pro Arg Glu Trp Pro Ala Gly Asp Arg Pro Arg
420 425 430

Arg Ala Gly Val Ser Ala Phe Gly Ile Ser Gly Thr Asn Ala His Leu
435 440 445

Ile Leu Glu Glu Ala Pro Pro Ala Asp Ala Val Ala Glu Glu Pro Glu
450 455 460

Phe Lys Gly Pro Val Pro Leu Val Val Ser Ala Gly Ser Pro Thr Ser
465 470 475 480

Leu Ala Ala Gln Ala Gly Arg Leu Ala Glu Val Leu Ala Ser Gly Gly
485 490 495

Val Ser Arg Ala Arg Leu Ala Ser Gly Leu Leu Ser Gly Arg Ala Leu
500 505 510

Leu Gly Asp Arg Ala Val Val Val Ala Gly Thr Asp Glu Asp Ala Val
515 520 525

Ala Gly Leu Arg Ala Leu Ala Arg Gly Asp Arg Ala Pro Gly Val Leu
530 535 540

Thr Gly Ser Ala Lys His Gly Lys Val Val Tyr Val Phe Pro Gly Gln
545 550 555 560

Gly Ser Gln Arg Leu Gly Met Gly Arg Glu Leu Tyr Asp Arg Tyr Pro
565 570 575

Val Phe Ala Thr Ala Phe Asp Glu Ala Cys Glu Gln Leu Asp Val Cys
580 585 590

Leu Ala Gly Arg Ala Gly His Arg Val Arg Asp Val Val Leu Gly Glu
595 600 605

Val Pro Ala Glu Thr Gly Leu Leu Asn Gln Thr Val Phe Thr Gln Ala
610 615 620

Gly Leu Phe Ala Val Glu Ser Ala Leu Phe Arg Leu Ala Glu Ser Trp
625 630 635 640

Gly Val Arg Pro Asp Val Val Leu Gly His Ser Ile Gly Glu Ile Thr
645 650 655

Ala Ala Tyr Ala Ala Gly Val Phe Ser Leu Pro Asp Ala Ala Arg Ile
660 665 670

Val Ala Ala Arg Gly Arg Leu Met Gln Ala Leu Ala Pro Gly Gly Ala
675 680 685

Met Val Ala Val Ala Ala Ser Glu Ala Glu Val Ala Glu Leu Leu Gly

690 695 700

Asp Gly Val Glu Leu Ala Ala Val Asn Gly Pro Ser Ala Val Val Leu
705 710 715 720

Ser Gly Asp Ala Asp Ala Val Val Ala Ala Ala Ala Arg Met Arg Glu
725 730 735

Arg Gly His Lys Thr Lys Gln Leu Lys Val Ser His Ala Phe His Ser
740 745 750

Ala Arg Met Ala Pro Met Leu Ala Glu Phe Ala Ala Glu Leu Ala Gly
755 760 765

Val Thr Trp Arg Glu Pro Glu Ile Pro Val Val Ser Asn Val Thr Gly
770 775 780

Arg Phe Ala Glu Pro Gly Glu Leu Thr Glu Pro Gly Tyr Trp Ala Glu
785 790 795 800

His Val Arg Arg Pro Val Arg Phe Ala Glu Gly Val Ala Ala Ala Thr
805 810 815

Glu Ser Gly Gly Ser Leu Phe Val Glu Leu Gly Pro Gly Ala Ala Leu
820 825 830

Thr Ala Leu Val Glu Glu Thr Ala Glu Val Thr Cys Val Ala Ala Leu
835 840 845

Arg Asp Asp Arg Pro Glu Val Thr Ala Leu Ile Thr Ala Val Ala Glu
850 855 860

Leu Phe Val Arg Gly Val Ala Val Asp Trp Pro Ala Leu Leu Pro Pro
865 870 875 880

Val Thr Gly Phe Val Asp Leu Pro Lys Tyr Ala Phe Asp Gln Gln His
885 890 895

Tyr Trp Leu Gln Pro Ala Ala Gln Ala Thr Asp Ala Ala Ser Leu Gly
900 905 910

Gln Val Ala Ala Asp His Pro Leu Leu Gly Ala Val Val Arg Leu Pro
915 920 925

Gln Ser Asp Gly Leu Val Phe Thr Ser Arg Leu Ser Leu Lys Ser His
930 935 940

Pro Trp Leu Ala Asp His Val Ile Gly Gly Val Val Leu Val Ala Gly
945 950 955 960

Thr Gly Leu Val Glu Leu Ala Val Arg Ala Gly Asp Glu Ala Gly Cys
965 970 975

Pro Val Leu Glu Glu Leu Val Ile Glu Ala Pro Leu Val Val Pro Asp
980 985 990

His Gly Gly Val Arg Ile Gln Val Val Val Gly Ala Pro Gly Glu Thr
995 1000 1005

Gly Ser Arg Ala Val Glu Val Tyr Ser Leu Arg Glu Asp Ala Gly Ala
1010 1015 1020

Glu Val Trp Ala Arg His Ala Thr Gly Phe Leu Ala Ala Thr Pro Ser
1025 1030 1035 1040

Gln His Lys Pro Phe Asp Phe Thr Ala Trp Pro Pro Pro Gly Val Glu
1045 1050 1055

Arg Val Asp Val Glu Asp Phe Tyr Asp Gly Leu Val Asp Arg Gly Tyr
1060 1065 1070

Ala Tyr Gly Pro Ser Phe Arg Gly Leu Arg Ala Val Trp Arg Arg Gly
1075 1080 1085

Asp Glu Val Phe Ala Glu Val Ala Leu Ala Glu Asp Asp Arg Ala Asp
1090 1095 1100

Ala Ala Arg Phe Gly Ile His Pro Gly Leu Leu Asp Ala Ala Leu His
1105 1110 1115 1120

Ala Gly Met Ala Gly Ala Thr Thr Thr Glu Glu Pro Gly Arg Pro Val
1125 1130 1135

Leu Pro Phe Ala Trp Asn Gly Leu Val Leu His Ala Ala Gly Ala Ser
1140 1145 1150

Ala Leu Arg Val Arg Leu Ala Pro Ser Gly Pro Asp Ala Leu Ser Val
1155 1160 1165

Glu Ala Ala Asp Glu Ala Gly Gly Leu Val Val Thr Ala Asp Ser Leu
1170 1175 1180

Val Ser Arg Pro Val Ser Ala Glu Gln Leu Gly Ala Ala Ala Asn His
1185 1190 1195 1200

Asp Ala Leu Phe Arg Val Glu Trp Thr Glu Ile Ser Ser Ala Gly Asp
1205 1210 1215

Val Pro Ala Asp His Val Glu Val Leu Glu Ala Val Gly Glu Asp Pro
1220 1225 1230

Leu Glu Leu Thr Gly Arg Val Leu Glu Ala Val Gln Thr Trp Leu Ala
1235 1240 1245

Asp Ala Ala Asp Asp Ala Arg Leu Val Val Val Thr Arg Gly Ala Val
1250 1255 1260

His Glu Val Thr Asp Pro Ala Gly Ala Ala Val Trp Gly Leu Ile Arg
1265 1270 1275 1280

Ala Ala Gln Ala Glu Asn Pro Asp Arg Ile Val Leu Leu Asp Thr Asp

1285 1290 1295

Gly Glu Val Pro Leu Gly Arg Val Leu Ala Thr Gly Glu Pro Gln Thr
1300 1305 1310

Ala Val Arg Gly Ala Thr Leu Phe Ala Pro Arg Leu Ala Arg Ala Glu
1315 1320 1325

Ala Ala Glu Ala Pro Ala Val Thr Gly Gly Thr Val Leu Ile Ser Gly
1330 1335 1340

Ala Gly Ser Leu Gly Ala Leu Thr Ala Arg His Leu Val Ala Arg His
1345 1350 1355 1360

Gly Val Arg Arg Leu Val Leu Val Ser Arg Arg Gly Pro Asp Ala Asp
1365 1370 1375

Gly Met Ala Glu Leu Thr Ala Glu Leu Ile Ala Gln Gly Ala Glu Val
1380 1385 1390

Ala Val Val Ala Cys Asp Leu Ala Asp Arg Asp Gln Val Arg Val Leu
1395 1400 1405

Leu Ala Glu His Arg Pro Asn Ala Val Val His Thr Ala Gly Val Leu
1410 1415 1420

Asp Asp Gly Val Phe Glu Ser Leu Thr Arg Glu Arg Leu Ala Lys Val
1425 1430 1435 1440

Phe Ala Pro Lys Val Thr Ala Ala Asn His Leu Asp Glu Leu Thr Arg
1445 1450 1455

Glu Leu Asp Leu Arg Ala Phe Val Val Phe Ser Ser Ala Ser Gly Val
1460 1465 1470

Phe Gly Ser Ala Gly Gln Gly Asn Tyr Ala Ala Ala Asn Ala Tyr Leu
1475 1480 1485

Asp Ala Val Val Ala Asn Arg Arg Ala Ala Gly Leu Pro Gly Thr Ser
1490 1495 1500

Leu Ala Trp Gly Leu Trp Glu Gln Thr Asp Gly Met Thr Ala His Leu
1505 1510 1515 1520

Gly Asp Ala Asp Gln Ala Arg Ala Ser Arg Gly Gly Val Leu Ala Ile
1525 1530 1535

Ser Pro Ala Glu Gly Met Glu Leu Phe Asp Ala Ala Pro Asp Gly Leu
1540 1545 1550

Val Val Pro Val Lys Leu Asp Leu Arg Lys Thr Arg Ala Gly Gly Thr
1555 1560 1565

Val Pro His Leu Leu Arg Gly Leu Val Arg Pro Gly Arg Gln Gln Ala
1570 1575 1580

Arg Pro Ala Ser Thr Val Asp Asn Gly Leu Ala Gly Arg Leu Ala Gly
1585 1590 1595 1600

Leu Ala Pro Ala Glu Gln Glu Ala Leu Leu Leu Asp Val Val Arg Thr
1605 1610 1615

Gln Val Ala Leu Val Leu Gly His Ala Gly Pro Glu Ala Val Arg Ala
1620 1625 1630

Asp Thr Ala Phe Lys Asp Thr Gly Phe Asp Ser Leu Thr Ser Val Glu
1635 1640 1645

Leu Arg Asn Arg Leu Arg Glu Ala Ser Gly Leu Lys Leu Pro Ala Thr
1650 1655 1660

Leu Val Phe Asp Tyr Pro Thr Pro Val Ala Leu Ala Arg Tyr Leu Arg
1665 1670 1675 1680

Asp Glu Leu Gly Asp Thr Val Ala Thr Thr Pro Val Ala Thr Ala Ala
1685 1690 1695

Ala Ala Asp Ala Gly Glu Pro Ile Ala Ile Val Gly Met Ala Cys Arg
1700 1705 1710

Leu Pro Gly Gly Val Thr Asp Pro Glu Gly Leu Trp Arg Leu Val Arg
1715 1720 1725

Asp Gly Leu Glu Gly Leu Ser Pro Phe Pro Glu Asp Arg Gly Trp Asp
1730 1735 1740

Leu Glu Asn Leu Phe Asp Asp Asp Pro Asp Arg Ser Gly Thr Thr Tyr
1745 1750 1755 1760

Thr Ser Arg Gly Gly Phe Leu Asp Gly Ala Gly Leu Phe Asp Ala Gly
1765 1770 1775

Phe Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln
1780 1785 1790

Arg Leu Leu Leu Glu Ala Ala Trp Glu Ala Leu Glu Gly Thr Gly Val
1795 1800 1805

Asp Pro Gly Ser Leu Lys Gly Ala Asp Val Gly Val Phe Ala Gly Val
1810 1815 1820

Ser Asn Gln Gly Tyr Gly Met Gly Ala Asp Pro Ala Glu Leu Ala Gly
1825 1830 1835 1840

Tyr Ala Ser Thr Ala Gly Ala Ser Ser Val Val Ser Gly Arg Val Ser
1845 1850 1855

Tyr Val Phe Gly Phe Glu Gly Pro Ala Val Thr Ile Asp Thr Ala Cys
1860 1865 1870

Ser Ser Ser Leu Val Ala Met His Leu Ala Gly Gln Ala Leu Arg Gln

1875 1880 1885

Gly Glu Cys Ser Met Ala Leu Ala Gly Gly Val Thr Val Met Gly Thr
1890 1895 1900

Pro Gly Thr Phe Val Glu Phe Ala Lys Gln Arg Gly Leu Ala Gly Asp
1905 1910 1915 1920

Gly Arg Cys Lys Ala Tyr Ala Glu Gly Ala Asp Gly Thr Gly Trp Ala
1925 1930 1935

Glu Gly Val Gly Val Val Val Leu Glu Arg Leu Ser Val Ala Arg Glu
1940 1945 1950

Arg Gly His Arg Val Leu Ala Val Leu Arg Gly Ser Ala Val Asn Ser
1955 1960 1965

Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser Gln Gln
1970 1975 1980

Arg Val Ile Arg Arg Ala Leu Ala Gly Ala Gly Leu Glu Pro Ser Asp
1985 1990 1995 2000

Val Asp Ile Val Glu Gly His Gly Thr Gly Thr Ala Leu Gly Asp Pro
2005 2010 2015

Ile Glu Ala Gln Ala Leu Leu Ala Thr Tyr Gly Lys Asp Arg Asp Pro
2020 2025 2030

Glu Thr Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Phe Gly His Thr
2035 2040 2045

Gln Ser Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Gln Ala Leu
2050 2055 2060

Arg His Gly Val Met Pro Pro Thr Leu His Val Asp Arg Pro Thr Ser
2065 2070 2075 2080

Gln Val Asp Trp Ser Ala Gly Ala Val Glu Val Leu Thr Glu Ala Arg
2085 2090 2095

Glu Trp Pro Arg Asn Gly Arg Pro Arg Arg Ala Gly Val Ser Ser Phe
2100 2105 2110

Gly Ile Ser Gly Thr Asn Ala His Leu Ile Ile Glu Glu Ala Pro Ala
2115 2120 2125

Glu Pro Gln Leu Ala Gly Pro Pro Pro Asp Gly Gly Val Val Pro Leu
2130 2135 2140

Val Val Ser Ala Arg Ser Pro Gly Ala Leu Ala Gly Gln Ala Arg Arg
2145 2150 2155 2160

Leu Ala Thr Phe Leu Gly Asp Gly Pro Leu Ser Asp Val Ala Gly Ala
2165 2170 2175

Leu Thr Ser Arg Ala Leu Phe Gly Glu Arg Ala Val Val Val Ala Asp
2180 2185 2190

Ser Ala Glu Glu Ala Arg Ala Gly Leu Gly Ala Leu Ala Arg Gly Glu
2195 2200 2205

Asp Ala Pro Gly Leu Val Arg Gly Arg Val Pro Ala Ser Gly Leu Pro
2210 2215 2220

Gly Lys Leu Val Trp Val Phe Pro Gly Gln Gly Thr Gln Trp Val Gly
2225 2230 2235 2240

Met Gly Arg Glu Leu Leu Glu Glu Ser Pro Val Phe Ala Glu Arg Ile
2245 2250 2255

Ala Glu Cys Ala Ala Ala Leu Glu Pro Trp Ile Gly Trp Ser Leu Phe
2260 2265 2270

Asp Val Leu Arg Gly Asp Gly Asp Leu Asp Arg Val Asp Val Leu Gln
2275 2280 2285

Pro Ala Cys Phe Ala Val Met Val Gly Leu Ala Ala Val Trp Ser Ser
2290 2295 2300

Ala Gly Val Val Pro Asp Ala Val Leu Gly His Ser Gln Gly Glu Ile
2305 2310 2315 2320

Ala Ala Ala Cys Val Ser Gly Ala Leu Ser Leu Glu Asp Ala Ala Lys
2325 2330 2335

Val Val Ala Leu Arg Ser Gln Ala Ile Ala Ala Lys Leu Ser Gly Arg
2340 2345 2350

Gly Gly Met Ala Ser Val Ala Leu Gly Glu Ala Asp Val Val Ser Arg
2355 2360 2365

Leu Ala Asp Gly Val Glu Val Ala Ala Val Asn Gly Pro Ala Ser Val
2370 2375 2380

Val Ile Ala Gly Asp Ala Gln Ala Leu Asp Glu Thr Leu Glu Ala Leu
2385 2390 2395 2400

Ser Gly Ala Gly Ile Arg Ala Arg Arg Val Ala Val Asp Tyr Ala Ser
2405 2410 2415

His Thr Arg His Val Glu Asp Ile Glu Asp Thr Leu Ala Glu Ala Leu
2420 2425 2430

Ala Gly Ile Asp Ala Arg Ala Pro Leu Val Pro Phe Leu Ser Thr Leu
2435 2440 2445

Thr Gly Glu Trp Ile Arg Asp Glu Gly Val Val Asp Gly Gly Tyr Trp
2450 2455 2460

Tyr Arg Asn Leu Arg Gly Arg Val Arg Phe Gly Pro Ala Val Glu Ala

2465 2470 2475 2480

Leu Leu Ala Gln Gly His Gly Val Phe Val Glu Leu Ser Ala His Pro
2485 2490 2495

Val Leu Val Gln Pro Ile Thr Glu Leu Thr Asp Glu Thr Ala Ala Val
2500 2505 2510

Val Thr Gly Ser Leu Arg Arg Asp Asp Gly Gly Leu Arg Arg Leu Leu
2515 2520 2525

Thr Ser Met Ala Glu Leu Phe Val Arg Gly Val Glu Val Asp Trp Thr
2530 2535 2540

Ser Leu Val Pro Pro Ala Arg Ala Asp Leu Pro Thr Tyr Ala Phe Asp
2545 2550 2555 2560

His Glu His Tyr Trp Leu Arg Ala Ala Asp Thr Ala Ser Asp Ala Val
2565 2570 2575

Ser Leu Gly Leu Ala Gly Ala Asp His Pro Leu Leu Gly Ala Val Val
2580 2585 2590

Gln Leu Pro Gln Ser Asp Gly Leu Val Phe Thr Ser Arg Leu Ser Leu
2595 2600 2605

Arg Ser His Pro Trp Leu Ala Asp His Ala Val Arg Asp Val Val Ile
2610 2615 2620

Val Pro Gly Thr Gly Leu Val Glu Leu Ala Val Arg Ala Gly Asp Glu
2625 2630 2635 2640

Ala Gly Cys Pro Val Leu Asp Glu Leu Val Ile Glu Ala Pro Leu Val
2645 2650 2655

Val Pro Arg Arg Gly Gly Val Arg Val Gln Val Ala Leu Gly Gly Pro
2660 2665 2670

Ala Asp Asp Gly Ser Arg Thr Val Asp Val Phe Ser Leu Arg Glu Asp
2675 2680 2685

Ala Asp Ser Trp Leu Arg His Ala Thr Gly Val Leu Val Pro Glu Asn
2690 2695 2700

Arg Pro Arg Gly Thr Ala Ala Phe Asp Phe Ala Ala Trp Pro Pro Pro
2705 2710 2715 2720

Glu Ala Lys Pro Val Asp Leu Thr Gly Ala Tyr Asp Val Leu Ala Asp
2725 2730 2735

Val Gly Tyr Gly Tyr Gly Pro Thr Phe Arg Ala Val Arg Ala Val Trp
2740 2745 2750

Arg Arg Gly Ser Gly Asn Thr Thr Glu Thr Phe Ala Glu Ile Ala Leu
2755 2760 2765

Pro Glu Asp Ala Arg Ala Glu Ala Gly Arg Phe Gly Ile His Pro Ala
2770 2775 2780

Leu Leu Asp Ala Ala Leu His Ser Thr Met Val Ser Ala Ala Ala Asp
2785 2790 2795 2800

Thr Glu Ser Tyr Gly Asp Glu Val Arg Leu Pro Phe Ala Trp Asn Gly
2805 2810 2815

Leu Arg Leu His Ala Ala Gly Ala Ser Val Leu Arg Val Arg Val Ala
2820 2825 2830

Lys Pro Glu Arg Asp Ser Leu Ser Leu Glu Ala Val Asp Glu Ser Gly
2835 2840 2845

Gly Leu Val Val Thr Leu Asp Ser Leu Val Gly Arg Pro Val Ser Asn
2850 2855 2860

Asp Gln Leu Thr Thr Ala Ala Gly Pro Ala Gly Ala Gly Ser Leu Tyr
2865 2870 2875 2880

Arg Val Asp Trp Thr Pro Leu Ser Ser Val Asp Thr Ser Gly Arg Val
2885 2890 2895

Pro Ser Trp Leu Pro Val Ala Thr Ala Glu Glu Val Ala Thr Leu Ala
2900 2905 2910

Asp Asp Val Leu Thr Gly Ala Thr Glu Ala Pro Ala Val Ala Val Met
2915 2920 2925

Glu Ala Val Ala Asp Glu Gly Ser Val Leu Ala Leu Thr Val Arg Val
2930 2935 2940

Leu Asp Val Val Gln Cys Trp Leu Ala Gly Gly Gly Leu Glu Gly Thr
2945 2950 2955 2960

Lys Leu Ala Ile Val Thr Arg Gly Ala Val Pro Ala Gly Asp Gly Val
2965 2970 2975

Val His Asp Pro Ala Ala Ala Ala Val Trp Gly Leu Val Arg Ala Ala
2980 2985 2990

Gln Ala Glu Asn Pro Asp Arg Ile Val Leu Leu Asp Val Glu Pro Glu
2995 3000 3005

Ala Asp Val Pro Pro Leu Leu Gly Ser Val Leu Ala Asp Gly Glu Pro
3010 3015 3020

Gln Val Ala Val Arg Gly Thr Thr Leu Ser Ile Pro Arg Leu Ala Arg
3025 3030 3035 3040

Ala Ala Arg Pro Asp Pro Ala Ala Gly Phe Lys Thr Arg Gly Pro Val
3045 3050 3055

Leu Val Thr Gly Gly Thr Gly Ser Leu Gly Gly Leu Val Ala Arg His

3060 3065 3070

Leu Val Glu Arg His Gly Val Arg Gln Leu Val Leu Ala Ser Arg Arg
3075 3080 3085

Gly Leu Asp Ala Glu Gly Ala Lys Asp Leu Val Thr Asp Leu Thr Ala
3090 3095 3100

Leu Gly Ala Asp Val Ala Val Ala Ala Cys Asp Val Ala Asp Arg Asp
3105 3110 3115 3120

Gln Val Ala Ala Leu Leu Thr Glu His Arg Pro Ser Ala Val Val His
3125 3130 3135

Thr Ala Gly Val Pro Asp Ala Gly Val Ile Gly Thr Val Thr Pro Asp
3140 3145 3150

Arg Leu Ala Glu Val Phe Ala Pro Lys Val Thr Ala Ala Arg His Leu
3155 3160 3165

Asp Glu Leu Thr Arg Asp Leu Asp Leu Asp Ser Phe Val Val Tyr Ser
3170 3175 3180

Ser Val Ser Ala Val Phe Met Gly Ala Gly Ser Gly Ser Tyr Ala Ala
3185 3190 3195 3200

Ala Asn Ala Tyr Leu Asp Gly Leu Met Ala His Arg Arg Ala Ala Gly
3205 3210 3215

Leu Pro Gly Gln Ser Leu Ala Trp Gly Leu Trp Asp Gln Thr Thr Gly
3220 3225 3230

Gly Met Ala Ala Gly Thr Asp Glu Ala Gly Arg Ala Arg Met Thr Arg
3235 3240 3245

Arg Gly Gly Leu Val Ala Met Lys Pro Ala Ala Gly Leu Asp Leu Phe
3250 3255 3260

Asp Ala Ala Ile Gly Ser Gly Glu Pro Leu Leu Val Pro Ala Gln Leu
3265 3270 3275 3280

Asp Leu Arg Gly Leu Arg Ala Glu Ala Ala Gly Gly Thr Glu Val Pro
3285 3290 3295

His Leu Leu Arg Gly Leu Val Arg Ala Gly Arg Gln Gln Ala Arg Ala
3300 3305 3310

Ala Ser Thr Val Glu Glu Asn Trp Ala Gly Arg Leu Ala Gly Leu Glu
3315 3320 3325

Pro Ala Glu Arg Gly Gln Val Leu Leu Glu Leu Val Arg Ala Gln Val
3330 3335 3340

Ala Gly Val Leu Gly Tyr Arg Ala Ala His Gln Val Asp Pro Asp Gln
3345 3350 3355 3360

Gly Leu Phe Glu Ile Gly Phe Asp Ser Leu Thr Ala Ile Glu Leu Arg
3365 3370 3375

Asn Arg Leu Arg Ala Arg Thr Glu Arg Lys Ile Ser Pro Gly Val Val
3380 3385 3390

Phe Asp His Pro Thr Pro Ala Leu Leu Ala Ala His Leu Asn Glu Leu
3395 3400 3405

Leu Arg Lys Lys Val
3410

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 226 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

```
Met Ala Ile Pro Tyr Ser Ser Leu Ala Tyr Glu Leu Arg Asp Ala Val
1               5                   10                  15

Asn Val Val Asp Leu Asp Glu Asp Asp Val Phe Val Thr Ser Ile Ala
            20                  25                  30

Glu Gly Gln Gly Gly Ala Cys Tyr His Leu Asn Arg Leu Phe His Arg
        35                  40                  45

Leu Leu Thr Glu Leu Gly Tyr Asp Val Thr Pro Leu Ala Gly Ser Thr
    50                  55                  60

Ala Glu Gly Arg Glu Thr Phe Gly Thr Asp Val Glu His Met Phe Asn
65                  70                  75                  80

Leu Val Thr Leu Asp Gly Ala Asp Trp Leu Val Asp Val Gly Tyr Pro
                85                  90                  95

Gly Pro Thr Tyr Val Glu Pro Leu Ala Val Ser Pro Ala Val Gln Thr
            100                 105                 110

Gln Tyr Gly Ser Gln Phe Arg Leu Val Glu Gln Glu Thr Gly Tyr Ala
        115                 120                 125

Leu Gln Arg Arg Gly Ala Val Thr Arg Trp Ser Val Val Tyr Thr Phe
    130                 135                 140

Thr Thr Gln Pro Arg Gln Trp Ser Asp Trp Lys Glu Leu Glu Asp Asn
```

145 150 155 160

Phe Arg Ala Leu Val Gly Asp Thr Thr Arg Thr Asp Thr Gln Glu Thr
165 170 175

Leu Cys Gly Arg Ala Phe Ala Asn Gly Gln Val Phe Leu Arg Gln Arg
180 185 190

Arg Tyr Leu Thr Val Glu Asn Gly Arg Glu Gln Val Arg Thr Ile Thr
195 200 205

Asp Asp Asp Glu Phe Arg Ala Leu Val Ser Arg Val Leu Ser Gly Asp
210 215 220

His Gly
225

Ciba-Geigy AG

CH-4002 Basel

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM	
Identification reference given by the DEPOSITOR: pRi7-3	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11114
II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION	
The microorganism identified under I. above was accompanied by: (X) a scientific description (X) a proposed taxonomic designation (Mark with a cross where applicable).	
III. RECEIPT AND ACCEPTANCE	
This International Depositary Authority accepts the microorganism identified under I. above, which was received by it on 1996-08-10 (Date of the original deposit)[1].	
IV. RECEIPT OF REQUEST FOR CONVERSION	
The microorganism identified under I above was received by this International Depositary Authority on (date of original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion).	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): U. Weiles Date: 1996-08-14

[1] Where Rule 6.4 (d) applies, such date is the date on which the status of international depositary authority was acquired.

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Ciba-Geigy AG

CH-4002 Basel

VIABILITY STATEMENT
issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: Ciba-Geigy AG Address: CH-4002 Basel	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11114 Date of the deposit or the transfer[1]: 1996-08-10
III. VIABILITY STATEMENT	
The viability of the microorganism identified under II above was tested on 1996-08-12 [2]. On that date, the said microorganism was (X)[3] viable ( )[3] no longer viable	
IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): U. Weis Date: 1996-08-14

[1] Indicate the date of original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).
[2] In the cases referred to in Rule 10.2(a) (ii) and (iii), refer to the most recent viability test.
[3] Mark with a cross the applicable box.
[4] Fill in if the information has been requested and if the results of the test were negative.

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Novartis AG

CH-4002 Basel

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:
pRi44-2	DSM 11655

II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I. above was accompanied by:

(X) a scientific description
(X) a proposed taxonomic designation

(Mark with a cross where applicable).

III. RECEIPT AND ACCEPTANCE

This International Depositary Authority accepts the microorganism identified under I. above, which was received by it on 1997-07-14 (Date of the original deposit)[1].

IV. RECEIPT OF REQUEST FOR CONVERSION

The microorganism identified under I above was received by this International Depositary Authority on (date of original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion).

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s) U. Weiß Date: 1997-07-15

[1] Where Rule 6.4 (d) applies, such date is the date on which the status of international depositary authority was acquired.

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Novartis AG

CH-4002 Basel

VIABILITY STATEMENT
issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: Novartis AG Address: CH-4002 Basel	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11655 Date of the deposit or the transfer[1]: 1997-07-14

III. VIABILITY STATEMENT

The viability of the microorganism identified under II above was tested on 1997-07-14 [2].
On that date, the said microorganism was

(X)[3] viable

( )[3] no longer viable

IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): U. Weihs Date: 1997-07-15

[1] Indicate the date of original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).
[2] In the cases referred to in Rule 10.2(a) (ii) and (iii), refer to the most recent viability test.
[3] Mark with a cross the applicable box.
[4] Fill in if the information has been requested and if the results of the test were negative.

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Novartis AG

CH-4002 Basel

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:
pNE95	DSM 11656

II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I. above was accompanied by:

(X) a scientific description
(X) a proposed taxonomic designation

(Mark with a cross where applicable).

III. RECEIPT AND ACCEPTANCE

This International Depositary Authority accepts the microorganism identified under I. above, which was received by it on 1997-07-14 (Date of the original deposit)[1].

IV. RECEIPT OF REQUEST FOR CONVERSION

The microorganism identified under I above was received by this International Depositary Authority on (date of original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion).

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): U. Weihs Date: 1997-07-15

[1] Where Rule 6.4 (d) applies, such date is the date on which the status of international depositary authority was acquired.

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Novartis AG

CH-4002 Basel

VIABILITY STATEMENT
issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: Novartis AG Address: CH-4002 Basel	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11656 Date of the deposit or the transfer[1]: 1997-07-14

III. VIABILITY STATEMENT

The viability of the microorganism identified under II above was tested on 1997-07-14 [2].
On that date, the said microorganism was

(X)[3] viable

( )[3] no longer viable

IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): U. Weiß Date: 1997-07-15

[1] Indicate the date of original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).
[2] In the cases referred to in Rule 10.2(a) (ii) and (iii), refer to the most recent viability test.
[3] Mark with a cross the applicable box.
[4] Fill in if the information has been requested and if the results of the test were negative.

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Novartis AG

CH-4002 Basel

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM	
Identification reference given by the DEPOSITOR: pNE112	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11657
II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION	
The microorganism identified under I. above was accompanied by: (X) a scientific description (X) a proposed taxonomic designation (Mark with a cross where applicable).	
III. RECEIPT AND ACCEPTANCE	
This International Depositary Authority accepts the microorganism identified under I. above, which was received by it on 1997-07-14 (Date of the original deposit)[1].	
IV. RECEIPT OF REQUEST FOR CONVERSION	
The microorganism identified under I above was received by this International Depositary Authority on (date of original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion).	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): U. Weihs Date: 1997-07-15

[1] Where Rule 6.4 (d) applies, such date is the date on which the status of international depositary authority was acquired.

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Novartis AG

CH-4002 Basel

VIABILITY STATEMENT
issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: Novartis AG Address: CH-4002 Basel	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11657 Date of the deposit or the transfer[1]: 1997-07-14

III. VIABILITY STATEMENT

The viability of the microorganism identified under II above was tested on 1997-07-14 [2].
On that date, the said microorganism was

(X)[3] viable

( )[3] no longer viable

IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): U. Weihs Date: 1997-07-15

[1] Indicate the date of original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).
[2] In the cases referred to in Rule 10.2(a) (ii) and (iii), refer to the most recent viability test.
[3] Mark with a cross the applicable box.
[4] Fill in if the information has been requested and if the results of the test were negative.

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<u>What is claimed is:</u>

1. A DNA fragment from the genome of *Amycolatopsis mediterranei* which comprises a DNA region which is involved directly or indirectly in the gene cluster responsible for rifamycin synthesis, including the adjacent DNA regions to the right and left which, by reason of their function in connection with rifamycin biosynthesis, qualify as constituent of this rifamycin gene cluster; and functional fragments, derivatives or constituents thereof.

2. A DNA fragment according to claim 1, which is directly or indirectly involved in the gene cluster responsible for rifamycin synthesis.

3. A DNA fragment according to claim 1, which comprises sequence portions which code for a polyketide synthase or an enzymatically active domain thereof.

4. A DNA fragment according to claim 1, which comprises SEQ ID NO 1 or SEQ ID NO 3 or at least 15 consecutive nucleotides therefrom.

5. A DNA fragment according to claim 1, wherein said fragment comprises one or more of the partial nucleotide sequences depicted in SEQ ID NOS 1 and/or 3, or functional fragments thereof, and all other DNA sequences in the vicinity of this sequence which can, by reason of homologies which are present, be regarded as structural or functional equivalents and are therefore able to hybridize with this sequence.

6. A DNA fragment according to claim 1, wherein said fragment comprises a nucleotide sequence selected from the group consisting of ORF A, B, C, D, E and F or functional fragments thereof, or encodes one or more of the proteins or polypeptides, or functional derivatives thereof, depicted in SEQ ID NOS 4 to 9.

7. A method for identifying, isolating and cloning a DNA fragment according to claim 1.

8. A method according to claim 7, which comprises the following steps:
   - setting up of a genomic gene bank,
   - screening of this gene bank with the assistance of the DNA sequences according to the invention, and
   - isolation of the clones identified as positive.

9. The use of a DNA fragment according to claim 1 in the production of ansamycins or precursors thereof; including those in which the aliphatic bridge is connected only at one end to the aromatic nucleus.

10. The use of a DNA fragment according to claim 1 in the production of rifamycin, rifamycin analogues or precursors thereof.

11. The use of a DNA fragment according to claim 1 for inactivating or modifying genes of ansamycin biosynthesis.

12. The use of a DNA fragment according to claim 1 for inactivating or modifying genes of rifamycin biosynthesis, or the biosynthesis of rifamycin analogues.

13. The use of a DNA fragment according to claim 1 for constructing mutated actinomycetes strains from which the natural rifamycin or ansamycin biosynthesis gene cluster in the chromosome has been partly or completely deleted.

14. The use of DNA fragments according to claim 1 for assembling a library of polyketide synthases.

15. The use of the polyketide synthases according to claim 14 for assembling a library of polyketides.

16. A polyketide synthase from *Amycolatopsis mediterranei* which is directly or indirectly involved in rifamycin synthesis; and functional constituents or domains thereof.

17. The use of the polyketide synthase according to claim 16 for synthesizing ansamycins.

18. The use of polyketide synthases according to claim 14 for synthesizing a library of ansamycins.

19. A hybrid vector comprising a DNA fragment according to claim 1.

20. A hybrid vector comprising an expression vector comprising a DNA fragment according to claim 1.

21. A host organism comprising a hybrid vector according to claim 19.

22. A hybridization probe comprising a DNA fragment according to claim 1.

23. The use of the hybridization probe according to claim 22 for identifying DNA fragments involved in the biosynthesis of ansamycins.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/04495

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/52 C12P17/18 C12P17/10 C12N9/00 C12N1/21
C12N15/70 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LAL, R. ET AL: "Rifamycins: strain improvement program" CRIT. REV. MICROBIOL. (1995), 21(1), 19-30 CODEN: CRVMAC;ISSN: 1040-841X, XP000615990 see the whole document ---	1
Y	MADON J ET AL: "TRANSFORMATION SYSTEM FOR AMYCOLATOPSIS -MEDITERRANEI DIRECT TRANSFORMATION OF MYCELIUM WITH PLASMID DNA." J BACTERIOL 173 (20). 1991. 6325-6331. CODEN: JOBAAY ISSN: 0021-9193, XP000615993 see the whole document ---	1
A	WO 87 03907 A (LUBRIZOL GENETICS INC) 2 July 1987 see claims --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 January 1998	13/01/1998
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Delanghe, L

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/04495

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 08548 A (UNIV LELAND STANFORD JUNIOR ;JOHN INNES CENTRE (GB)) 30 March 1995 see claims -----	1

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ational Application No
PCT/EP 97/04495

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8703907 A	02-07-87	AU 598516 B	28-06-90
		AU 6835487 A	15-07-87
		EP 0262154 A	06-04-88
		EP 0463707 A	02-01-92
WO 9508548 A	30-03-95	US 5672491 A	30-09-97
		AU 678058 B	15-05-97
		AU 7731794 A	10-04-95
		CA 2171629 A	30-03-95
		EP 0725778 A	14-08-96
		JP 9505983 T	17-06-97